

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 16 February 2001 (16.02.01)	
International application No. PCT/EP00/05783	Applicant's or agent's file reference 17394PC WAR
International filing date (day/month/year) 07 June 2000 (07.06.00)	Priority date (day/month/year) 07 June 1999 (07.06.99)
Applicant CALVET, Alain et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
15 December 2000 (15.12.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

POCHART, François
Cabinet Hirsch-Pochart
34, rue de Bassano
F-75008 Paris
FRANCE

Date of mailing (day/month/year) 03 January 2002 (03.01.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 17394PC WAR	
International application No. PCT/EP00/05783	International filing date (day/month/year) 07 June 2000 (07.06.00)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address HAMON, Jacques 6, allée du Bellay F-91400 Orsay France	State of Nationality FR	State of Residence FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address HAMON, Jacques 39, route de la Touche F-91530 Saint Maurice Montcouronne France	State of Nationality FR	State of Residence FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input checked="" type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Antonia MULLER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

POCHART, François
Cabinet Hirsch-Pochart
34, rue de Bassano
F-75008 Paris
FRANCE

TECH CENTER 1600/2900

MAR 13 2002

RECEIVED

Date of mailing (day/month/year) 03 January 2002 (03.01.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 17394PC WAR	
International application No. PCT/EP00/05783	International filing date (day/month/year) 07 June 2000 (07.06.00)

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Name and Address

HAMON, Jacques
6, allée du Bellay
F-91400 Orsay
France

State of Nationality

FR

State of Residence

FR

Telephone No.

Facsimile No.

Teleprinter No.

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Name and Address

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F-91530 Saint Maurice Montcouronne
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<input checked="" type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Antonia MULLER

Telephone No.: (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 17394PC WAR	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/05783	International filing date (day/month/year) 07/06/2000	(Earliest) Priority Date (day/month/year) 07/06/1999
Applicant WARNER-LAMBERT COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D221/20 A61K31/438 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 414 289 A (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27) claims	1-13
Y	WO 94 17045 A (MERCK & CO INC ;HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04) claims	1-13
Y	US 5 439 914 A (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08) claims	1-13
A	EP 0 431 943 A (MERCK & CO INC) 12 June 1991 (1991-06-12) claims	1-13
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 October 2000

Date of mailing of the international search report

- 12/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25604 A (SPRINGER MARTIN S ;MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18) claims ---	1-13
P,A	US 6 013 644 A (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11) claims -----	1-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/05783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05783

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0414289	A	27-02-1991	AT 101854 T	15-03-1994
			AU 628612 B	17-09-1992
			AU 5984490 A	31-01-1991
			CA 2021736 A	27-01-1991
			DE 69006799 D	31-03-1994
			DE 69006799 T	11-08-1994
			DK 414289 T	11-04-1994
			ES 2062303 T	16-12-1994
			JP 3184959 A	12-08-1991
			NO 903315 A	28-01-1991
			NZ 234557 A	23-12-1992
			PT 94806 A	20-03-1991
			ZA 9005841 A	26-06-1991
WO 9417045	A	04-08-1994	AT 169001 T	15-08-1998
			AU 693087 B	25-06-1998
			AU 6126894 A	15-08-1994
			CA 2154569 A	04-08-1994
			DE 69412067 D	03-09-1998
			DE 69412067 T	25-03-1999
			DK 681571 T	23-11-1998
			EP 0681571 A	15-11-1995
			ES 2119174 T	01-10-1998
			JP 8505880 T	25-06-1996
			US 5869496 A	09-02-1999
US 5439914	A	08-08-1995	AU 1920895 A	04-09-1995
			CA 2182733 A	24-08-1995
			EP 0745086 A	04-12-1996
			JP 9509177 T	16-09-1997
			WO 9522548 A	24-08-1995
EP 0431943	A	12-06-1991	AT 168377 T	15-08-1998
			AU 6329794 A	21-07-1994
			AU 6787390 A	13-06-1991
			CA 2031633 A	09-06-1991
			CN 1053613 A	07-08-1991
			CN 1110685 A	25-10-1995
			DE 69032480 D	20-08-1998
			DE 69032480 T	06-05-1999
			ES 2118715 T	01-10-1998
			FI 906045 A	09-06-1991
			JP 2016496 C	19-02-1996
			JP 4217960 A	07-08-1992
			JP 7047576 B	24-05-1995
			NO 905306 A	10-06-1991
			NZ 236315 A	27-09-1994
			PT 96126 A	30-09-1991
			US 5633247 A	27-05-1997
			US 5206240 A	27-04-1993
			ZA 9009836 A	25-09-1991
WO 9825604	A	18-06-1998	AU 5604998 A	03-07-1998
			US 6013664 A	11-01-2000
US 6013644	A	11-01-2000	NONE	

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 17394PC WAR

Box No. I	TITLE OF INVENTION TRICYCLIC ANALGESICS	
Box No. II	APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) WARNER-LAMBERT COMPANY 201 Tabor Road MORRIS PLAINS, NJ 07950 USA		<input type="checkbox"/> This person is also inventor. Telephone No. Facsimile No. Teleprinter No.
State (that is, country) of nationality: US		State (that is, country) of residence: US
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box		
Box No. III	FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) CALVET Alain 3475 Creekside Drive Ann Arbor, MI 48105 USA		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
State (that is, country) of nationality: FR		State (that is, country) of residence: US
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box		
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.		
Box No. IV	AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:		<input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) POCHART François CABINET HIRSCH-POCHART 34, rue de Bassano 75008 PARIS FRANCE		Telephone No. 01.53.23.92.12 Facsimile No. 01.47.23.49.13 Teleprinter No.
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.		

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>JACOBELLI Henri 65, avenue du Général de Gaulle 91550 PARAY-VIEILLE-POSTE FRANCE</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>PUAUD Jocelyne 29, chemin de la mère Dieu 91310 MONTLHERY FRANCE</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>ROMAN François J. 11, allée Pierre Fresnay 94400 VITRY-SUR-SEINE FRANCE</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><small>Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</small></p> <p>HAMON Jacques 6, allée Du Bellay 91400 ORSAY FRANCE</p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p>
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.</p>	

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
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State <i>(that is, country)</i> of nationality: FR	State <i>(that is, country)</i> of residence: FR
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p>Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i></p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i></p>
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p>Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i></p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i></p>
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p>Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i></p>	<p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only <i>(If this check-box is marked, do not fill in below.)</i></p>
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
<p>This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box</p>	
<p><input type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.</p>	

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Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input type="checkbox"/> LS Lesotho |
| <input type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input type="checkbox"/> AT Austria | <input type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | |
| <input type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> CA Canada | <input type="checkbox"/> MW Malawi |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input type="checkbox"/> PT Portugal |
| <input type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input type="checkbox"/> DK Denmark | <input type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input type="checkbox"/> SE Sweden |
| <input type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
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| <input type="checkbox"/> GH Ghana | <input type="checkbox"/> TM Turkmenistan |
| <input type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
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| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> DZ Algeria |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> AG Antigua & Barbuda |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

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Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.


2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Box IV - OTHER AGENTS

ROCHET Michel
CORTEY Pierre
Cabinet HIRSCH-POCHART
34, rue de Bassano
75008 PARIS
FRANCE

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Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) June 07, 1999	US 60/137,868	US		
item (2)				
item (3)				
<input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):				
<i>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</i>				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		
ISA/ EP				
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 6 description (excluding sequence listing part) : 48 claims : 10 abstract : 1 drawings : sequence listing part of description : Total number of sheets 65		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):		
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: English		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). POCHART François 				

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA/	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

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PCT

FEE CALCULATION SHEET Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference 17394PC WAR 163

Applicant
WARNER-LAMBERT COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE 102,00 EUR T

2. SEARCH FEE 945,00 EUR S

International search to be carried out by _____
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 65 sheets.

first 30 sheets 409,00 EUR b1

35 x 9,00 EUR = 315,00 EUR b2
remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B 724,00 EUR B

Designation Fees

The international application contains 57 designations.

8 x 88,00 EUR = 704,00 EUR D

number of designation fees payable (maximum 8) amount of designation fee

Add amounts entered at B and D and enter total at I 1428,00 EUR I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) P

5. TOTAL FEES PAYABLE 2475,00 EUR

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below) ☐ bank draft ☐ coupons
☐ cheque ☐ cash ☐ other (specify):
☐ postal money order ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ EP ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2 804 0070

June 07, 2000

Deposit Account No.

Date (day/month/year)

Signature

POCHART François

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PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

WARNER-LAMBERT COMPANY, 201 Tabor Road, MORRIS PLAINS, NJ 07950 - USA

hereby appoints (appoint) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAU-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

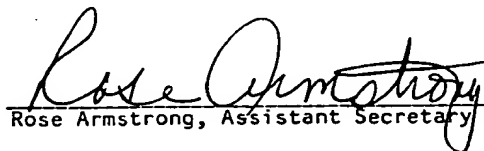
Applicant's or agent's file reference: 17394PC WAR

International application number (if already available):

filed with the following Office OEB as receiving Office
and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

Date:


Rose Armstrong, Assistant Secretary

April 17, 2000

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PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

CALVET Alain, 3475 Creekside Drive, ANN ARBOR MI 48105 USA

hereby appoints (appoint) the following person as:

☒ agent

☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAU-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

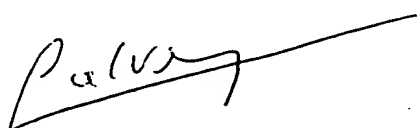
Applicant's or agent's file reference: 17394PC WAR

• International application number (if already available):

filed with the following Office _____ OEB _____ as receiving Office
and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

Date:


April 17th 2013 Alain Calvet

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PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (Names should be indicated as they appear in the request):

GROUHEL Agnes, 2 rue des Peupliers, 92190 MEUDON - FRANCE
HAMON Jacques, 6 Allée du Bellay, 91400 ORSAY - FRANCE
JACOBELLI Henri, 65 Avenue du Général de Gaulle, 91550 PARAY VIEILLE POSTE - FRANCE
PUAUD Jocelyne, 29 Chemin de la Mère Dieu, 91310 MONTLHERY - FRANCE
ROMAN François Joseph, 11 Allée Pierre-Fresnay, 94400 VITRY-SUR-SEINE - FRANCE

hereby appoints (appoint) the following person as:



agent



common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAUX-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before



all the competent International Authorities



the International Searching Authority only



the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

Applicant's or agent's file reference:

17394PC WAR

International application number (if already available):

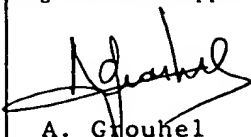
filed with the following Office

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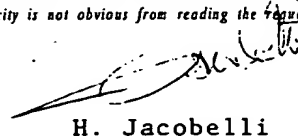
as receiving Office

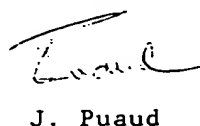
and to make or receive payments on behalf of the undersigned.


Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):


A. Grouhel


J. Hamon


H. Jacobelli


J. Puaud


F.-J. Roman

Date: 22 Mars 2000

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 17394PC WAR		FOR FURTHER ACTION. See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/05783	International filing date (day/month/year) 07/06/2000	Priority date (day/month/year) 07/06/1999	
International Patent Classification (IPC) or national classification and IPC C07D221/00			
Applicant WARNER-LAMBERT COMPANY et al.			

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 8 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 15/12/2000	Date of completion of this report 29.08.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cortés, J. Telephone No. +49 89 2399 8206 

Express Mail No. EF378134286US

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05783

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, pages:

1-48 as originally filed

Claims, No.:

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10-13.

because:

☒ the said international application, or the said claims Nos. 10-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 2, 4, 6-8, 10-13
 No: Claims 1, 3, 5, 9

Inventive step (IS) Yes: Claims
 No: Claims 1-13

Industrial applicability (IA) Yes: Claims 1-9

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/05783

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05783

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 10-13 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the search report are referred to in this communication:

- D1: EP-A-0 414 289 (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27)
- D2: WO 94 17045 A (MERCK & CO INC; HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04)
- D3: US-A-5 439 914 (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08)
- D4: EP-A-0 431 943 (MERCK & CO INC) 12 June 1991 (1991-06-12)
- D5: WO 98 25604 A (SPRINGER MARTIN S; MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18)

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05783

Novelty

Present compounds are encompassed by the generic formula in D5 (D5: e.g. claim 1, column 52), and the starting compound in example 78, namely spiro(6-methoxyindan-1-one[2.4]piperidine) is within the scope of present claims 1, 3, 5 (D5: e.g. page 85 and spiro(indane-1-one[2.4]piperidine) derivatives in claims 3 and 9, columns 57 and 62).

Therefore, present claims 1, 3, 5 and 9 are not novel in view of D5 (Article 33(3) PCT).

Present compounds differ from the ones in D1 in the spiro(cycloalkaphenyl[2.4]piperidine) structure. The compounds of D1 have a spiro(cycloalkaphenyl[1.4]piperidine) structure (D1: e.g. claim 1, page 25).

Present compounds are encompassed by the generic formula in D2 (D2: e.g. claim 1, page 69), but differ from close related sub-groups or specific compounds in D2 in the above mentioned structural feature (D2: e.g. claims 11 and 12, pages 95-101).

Present compounds differ from the compounds in D3 in that both R¹ and R² can be hydrogen, or, provided that one of both is not hydrogen, in that this substituent is then in 1-position of the cycloalkaphenyl and not in 4-position (D3: e.g. claim 1, column 29).

Present compounds are encompassed by the generic formula in D4 (D4: e.g. claim 1, page 155), but differ from close related sub-groups or specific compounds in D4 in the spiro(cycloalkaphenyl[2.4]piperidine) structure (D4: e.g. claims 2-3, 7-8, pages 159, 161-162). The closest related compounds in D4 have a spiro(cycloalkaphenyl[2.3]piperidine) structure (D4: e.g. examples 501-502, page 149).

Present compounds are a novel specific selection of the compounds generically disclosed in D2 and D4.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05783

Inventive Step

D2 discloses structurally related compounds for the same medical use and can be regarded as the closest prior art.

Since present compounds are encompassed by the generic formula in D2, it was obvious they would have analgesic properties.

The problem of the invention must therefore be formulated as the provision of new analgesics with unexpected properties or advantages when compared to the closest related compounds known from D2.

In the absence of any such evidence, present application does not comply with the requirements of inventiveness according to Article 33(3) PCT.

Industrial Applicability

For the assesment of the present claims 10-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can be dependent upon the formulation of the claims. The EPO, for instance, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Reference is made to the following P-document:

D6: US-A-6 013 644 (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11)

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/05783

The priority documents pertaining to the present application were not examined at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-documents ... cited in the international search report could become relevant to assess whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

Re Item VII

Certain defects in the international application

The description does not mention the closest prior art represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

Re Item VIII

Certain observations on the international application

Many compounds of claims 6-8 are listed several times (e.g. 2. compound in claim 6; conciseness, Article 6 PCT).

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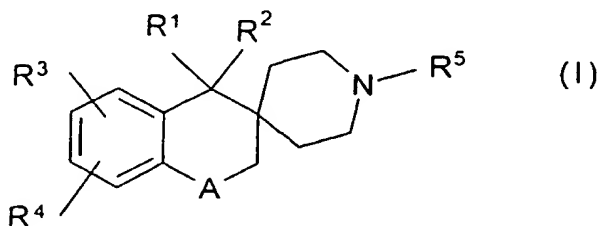
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRICYCLIC ANALGESICS



(57) Abstract: A tricyclic compound of Formula (I); wherein: R¹ is hydrogen or hydroxy; R² is hydrogen or hydroxy; or R¹ and R² together are oxygen; A is a bond, CH₂, CH, CH₃, CH₂, CH₂ or C(CH₃)₂; R³ and R⁴ are the same or different and are hydrogen, halo, C₁-C₆ alkyl, C₁-C₄ alkoxy, trifluoromethyl, NO₂, COR⁶, COOR⁶ or NR⁶R⁷, wherein R⁶ and R⁷ are the same or different and are hydrogen, C₁-C₆ alkyl or benzyl; R⁵ is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ cycloalkyl, (O=C)-C₁-C₆ alkyl, (O=C)-C₂-C₆ alkenyl, (O=C)-C₃-C₆ cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups

can be substituted by 1, 2 or 3 groups selected from halo, C₃-C₆ cycloalkyl, phenyl or substituted phenyl, and salts thereof, are particularly useful for treating, among other indications, neuropathic pain and other CNS disorders.

WO 00/075116 A3

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D221/20 A61K31/438 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 414 289 A (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27) claims	1-13
Y	WO 94 17045 A (MERCK & CO INC ;HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04) claims	1-13
Y	US 5 439 914 A (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08) claims	1-13
A	EP 0 431 943 A (MERCK & CO INC) 12 June 1991 (1991-06-12) claims	1-13
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

3 October 2000

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/05783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25604 A (SPRINGER MARTIN S ;MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18) claims -----	1-13
P,A	US 6 013 644 A (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11) claims -----	1-13

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/05783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/05783

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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TRICYCLIC ANALGESICS

FIELD OF THE INVENTION

The invention relates to organic compounds characterized as having a fused bicyclic ring system substituted with a spiro nitrogen-containing third ring.
5 The compounds are effective for treating seizures and chronic pain in mammals.

BACKGROUND OF THE INVENTION

Although chronic pain is a frequent condition in the population, its pathophysiology is not well understood. One possibility is that nociceptive spinal sensory neurons generate inappropriate activity after injury. Spinal sensory
10 neurons become hyperexcitable and generate spontaneous impulses after injury in experimental animals, and in humans. Matzner and Devor (1992) proposed that the hyperexcitability associated with chronic pain results from an increase of Na channel density at the site of injury. It has also been hypothesized that, after nerve injury, changes in the kinetics and voltage-dependent characteristics of Na currents
15 contribute to the ectopic impulse generation and hyperexcitability of spinal sensory neurons. Dorsal root ganglion (DRG) neurons possess a complex mix of Na currents, including a fast tetrodotoxin-sensitive (TTX-S) current and a slow TTX-resistant (TTX-R) current. In rat DRG neurons, PGE₂, adenosine and serotonin, three agents that produce hyperalgesia in vivo, increase the magnitude
20 of the TTX-R current, and shift its conductance/voltage relationship in a hyperpolarized direction (Gold *et al.*, 1996). Following nerve injury, TTX-R currents are down regulated in DRG neurons, and, in the same animals, TTX-S currents are upregulated (Cummings and Waxman, 1997). Using a Na channel specific antibody, Devor *et al.* (1993) evidenced an accumulation of Na channels
25 in the neuroma resulting from a nerve section; the accumulation of Na channels at injured axonal tips may explain the ectopic channel excitability and the resulting

pain and paresthesia which frequently complicate peripheral nerve injury in humans.

Injury to the axons of spinal sensory neurons appear to modify Na currents, substantially altering their excitability; Thus, selective blockers of Na channels
5 can be used for the prevention or treatment of chronic pain in mammals. Sodium channel blockers have been shown effective in chronic pain syndromes, including trigeminal neuralgia, diabetic neuropathy, migraine prophylaxis and cancer pain (review by McQuay *et al.*, 1995, British Medical Journal, 1995; 311: 1047-1052, and references cited therein).

10 However, pain due to acute or chronic nerve injury is difficult to treat, and is often resistant to conventional analgesics. Such compounds include some local anesthetics and anticonvulsants, for example lidocaine, etidocaine, benzocaine, tetracain, riluzole, phenytoin, and gabapentin. Most of them, even though such agents modulate Na channels, have limited clinical use because of high risks of
15 adverse events. Lidocaine, for example, can cause cardiovascular collapse and resultant cardiac arrest. Benzocaine, can cause respiratory distress, as well as skin rash, erythema and oedema. The use of phenytoin for seizure disorders can result in hyperglycemia.

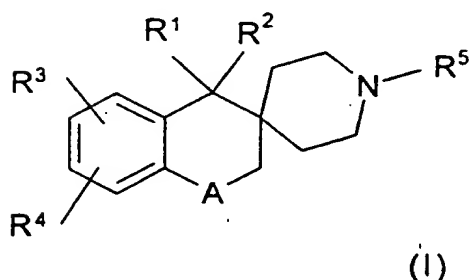
20 Because there is no effective chemical treatment for neuropathic pain, e.g. chronic pain, and since such pain is typically associated with diseases such as cancer, as well as severe physical injuries and diabetic neuropathy, the need continues to find compounds which can be utilized clinically without resulting in severe adverse events.

SUMMARY OF THE INVENTION

The inventors have now discovered a series of tricyclic compounds which are potent antagonists of neuronal Na channels. The compounds are characterized as fused bicyclic ring systems having a spiro third ring substitution.

5

The invention therefore provides tricyclic compounds of Formula I:



wherein:

- 10 R^1 is hydrogen or hydroxy;
 R^2 is hydrogen or hydroxy; or
 R^1 and R^2 together are oxygen ;
A is a bond, CH_2 , CH CH_3 , CH_2 CH_2 or $C(CH_3)_2$;
 R^3 and R^4 are the same or different and are hydrogen, halo, C_1 - C_6 alkyl,
15 C_1 - C_4 alkoxy, trifluoromethyl, NO_2 , COR^6 , $COOR^6$ or NR^6R^7 , wherein R^6 and
 R^7 are the same or different and are hydrogen, C_1 - C_6 alkyl or benzyl ;
 R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, $(O=C)$ - C_{1-6} alkyl,
 $(O=C)$ - C_{2-6} alkenyl, $(O=C)$ - C_{3-6} cycloalkyl, wherein said alkyl, alkenyl and
cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3 - C_6
20 cycloalkyl, phenyl or substituted phenyl,
and the pharmaceutically acceptable salts thereof.

The compounds of the invention are useful in the clinical management and treatment of various conditions such as seizure disorders, epilepsy, neuroprotection, preferably for conditions such as cerebral ischemia, hypoxia and head trauma, local anesthesia, pain, preferably acute, chronic, neuropathic, visceral and somatic pain, irritable bowel syndrom (IBS), the treatment of drug dependence, migraine and obsessional compulsive disorders.

Preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1 - C_6 alkyl, optionally substituted with phenyl or a C_3 - C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is C_1 - C_6 alkyl, optionally substituted with phenyl or a C_3 - C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1 - C_6 alkyl, optionally substituted with phenyl or a C_3 - C_6 cycloalkyl group and R^3 is hydrogen or C_1 - C_4 alkoxy.

Most preferred compounds of the invention are compounds of Formula I wherein R^1 and R^2 together are oxygen and A is CH_2 .

Other most preferred compounds are those of formula I wherein R^5 is H, C_1 - C_6 alkyl, optionally substituted with phenyl or a C_3 - C_6 cycloalkyl group and R^3 is hydrogen or C_1 - C_4 alkoxy.

Another embodiment of this invention is a pharmaceutical formulation comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier or diluent.

A further embodiment of the present invention is a method for treating a mammal suffering from pain and in need of treatment, comprising administering an effective amount of a compound of Formula I.

Still another embodiment of the invention is a method for treating a seizure disorder in a mammal in need of treatment, comprising administering a compound of Formula I.

5 Methods of treatment of all the further indications referred to above also fall within the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C₁-C₆ alkyl" means a straight or branched carbon chain made up of from one to six carbon atoms. Examples of C₁-C₆ alkyl groups include methyl, ethyl, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl and *n*-hexyl.

"C₁-C₆ alkoxy" means the foregoing alkyl groups bonded through oxygen, for example methoxy, isopropoxy, and *n*-hexyloxy.

"C₂-C₆ alkenyl" means a straight or branched carbon chain having from two to six carbon atoms, with one carbon-carbon double bond present in the chain. Examples include ethenyl, 2-propenyl, 1-methyl-3-pentenyl, 1-ethyl-2-butenyl, and 5-hexenyl.

"C₃-C₆ cycloalkyl" means a non-aromatic cyclic ring having from three to six carbon atoms, examples being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The foregoing alkyl, alkenyl and cycloalkyl groups may be substituted by 1, 2 or 3 groups selected from halo, unsubstituted C₃-C₆ cycloalkyl, phenyl or substituted phenyl. "Halo" means chloro, bromo, fluoro and iodo. "Substituted phenyl" means a phenyl group having 1, 2 or 3 substituents selected from halo, hydroxy, nitro, unsubstituted C₁-C₆ alkyl, unsubstituted C₁-C₆ alkoxy, and NH₂.

Examples of C₁-C₆ alkyl groups substituted with cycloalkyl thus include cyclopropylmethyl, 1-cyclobutylethyl, 3-cyclohexylbutyl and 3,3-dicyclohexylpropyl. Alkyl groups substituted with halo include chloromethyl, 1,2-dibromoethyl, trifluoromethyl, and 1-bromo-3-chloro-6-iodohexyl. Alkyl groups substituted with phenyl or with substituted phenyl include benzyl, 1-phenylpropyl, 1-methyl-3-phenyl-butyl, 3-chlorophenylmethyl, 2,3-dimethoxybenzyl, 3-(2-methyl-5-fluoro-6-nitrophenyl)-butyl, and 3,3-diphenylpropyl.

Examples of substituted C₂-C₆ alkenyl groups include 2-cyclobutylethenyl, 3-phenyl-2-butenyl, 1,1-dimethyl-3-chloro-3-butenyl, 4,4-diphenyl-3-butenyl, 2-

-7-

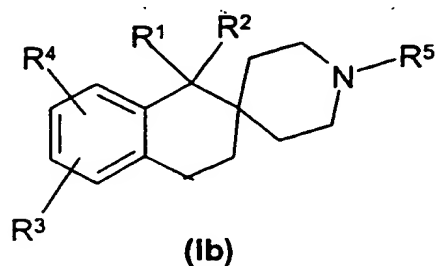
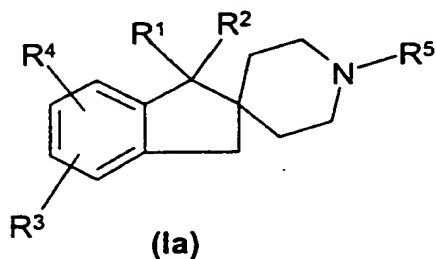
(3-chlorophenyl)-3-cyclobutyl-4-hexenyl, and 1,2-difluoro-3-(2-phenyl-cyclobutyl)-4-pentenyl.

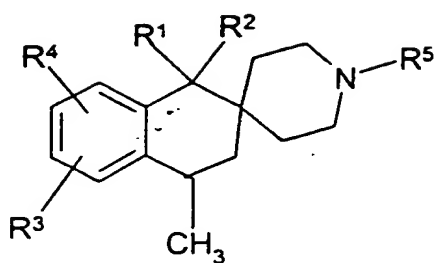
5 Examples of substituted C_3 - C_6 cycloalkyl groups include 3-cyclopentylcyclohexyl, 2-phenylcyclobutyl, 3-chlorocyclopentyl, 2,2-dibromo-3-nitro-cyclohexyl, and 2,2-di-(3-methoxyphenyl)-cyclopropyl.

Examples of substituted C_1 - C_6 alkoxy groups include trichloromethoxy, cyclopropylmethoxy, 1-methyl-2-phenylpropoxy and 2,3-di-(2,4-dinitrophenyl)-hexyloxy.

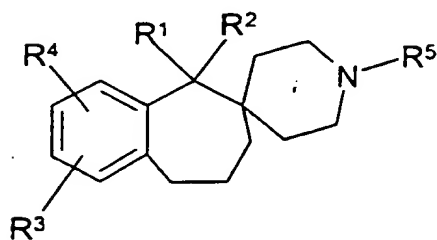
10 The alkyl, alkenyl and cycloalkyl substituent groups can be bonded through a carbonyl ($O=C$) group. Examples include acetyl, pivaloyl, 1-oxo-3-pentenyl, 1-oxocyclobutylmethyl, 1-oxo-3-phenyl-4-cyclohexylpentyl, and 1-oxo-(3-phenylcyclopentyl)-methyl.

15 "-A-" in Formula I is defined as a bond, $-CH_2-$, $-CH-CH_3$, $-CH(CH_3)_2$ and $-CH_2CH_2-$; the invention compounds can thus have the following general structures:





(Ic)



(Id)

Preferred compounds of the present invention include the following:

- 5 3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 10 1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-
- 15 2(1*H*),4'-piperidine];
- 1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
- 20 1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

- 1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 5 1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 10 1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;
- 3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 15 1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];
- 20 1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;
- 1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 25 1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 30 1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

- 1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
5 piperidine ;
1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
10 1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-
15 piperidine ;
1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-
2(1H),4'-piperidine ;
1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
20 1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
25 piperidine ;
1'-(2-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-
piperidine ;
30 1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-
2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

5 1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

10 1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

15 1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

20 1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

25 1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

30 6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

-12-

- 6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-
5 piperidine ;
6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and
6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.
10 3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

More preferred compounds of the invention include the following:

- 15 1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
20 1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1H),4'-
25 piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
30 1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

- 1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;
- 5 1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];
- 1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;
- 1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 10 6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 15 1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 20 1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 25 1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 30 1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

- 1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 5 1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 10 1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 15 1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 20 1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 25 1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 30 6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine).

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

5 Most preferred compounds of the invention include the following:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-

10 piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

15 1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

20 1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

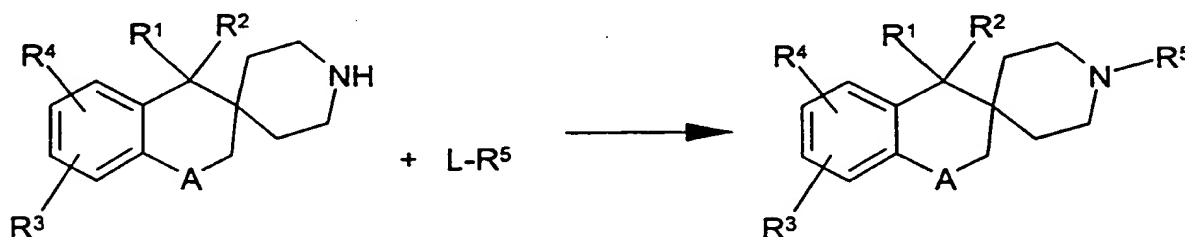
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The compounds of Formula I are characterized by being bicyclic rings having a spiro ring as a substituent group. The spiro ring contains a nitrogen atom (i.e. N-R⁵), which can be basic in nature when R⁵ is a group such as alkyl, alkenyl or cycloalkyl. Such basic compounds readily form pharmaceutically acceptable salts by reaction with common inorganic and organic acids. Typical acids utilized

30 to form the pharmaceutically acceptable salts of the invention include hydro-

chloric, sulfuric, sulfamic, phosphoric, citric, succinic, glutamic, maleic, lactic, tartaric, *p*-toluenesulfonic, benzoic, oxalic and salicylic acid. The salts are prepared by simply contacting the spiro base with the appropriate acid, generally in a solvent such as methanol or diethyl ether. The salts generally are highly crystalline, readily precipitate, and are recovered by filtration. They can be further purified if desired by recrystallization from common solvents such as methanol, ethyl acetate, acetone and tetrahydrofuran.

The invention compounds of Formula I are readily prepared by methodologies well known in the art of organic chemistry. It is preferred to simply first prepare a compound wherein R^5 is hydrogen, and then react this compound with R^5 -alkylating or -acylating agents. Such reaction is shown in scheme 1 below:

Scheme 1

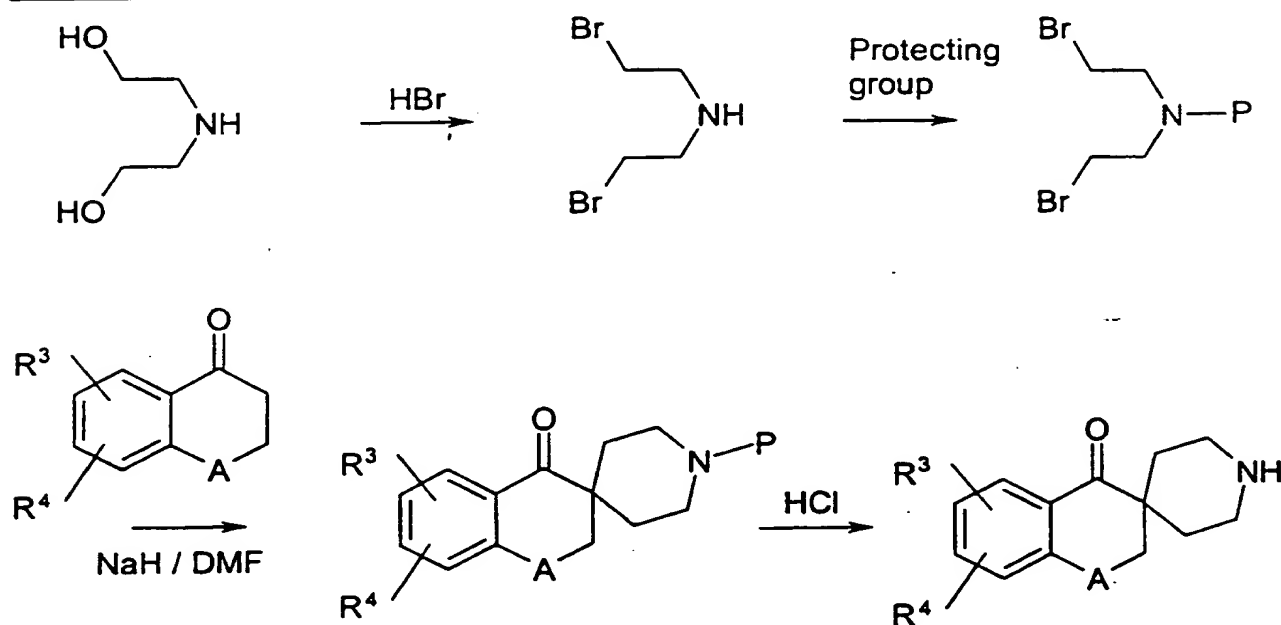
where R^1 , R^2 , R^3 , R^4 , and A have the meanings given above, and "L" is a normal leaving group (e.g. halo such as chloro or bromo, or a silyl derivative such as trimethylsilyl).

The foregoing reaction is carried out by combining approximately equimolar quantities of the spiro amine with the alkylating or acylating agent (i.e. $L-R^5$), generally in an unreactive organic solvent such as tetrahydrofuran, dimethylsulfoxide, or N,N-dimethylformamide. A base such as triethylamine or $NaHCO_3$ can be utilized to act as an acid scavenger if desired. The reaction typically is substantially complete after about 2 - 20 h, when conducted at a temperature is about 25°C to about 60°C. The product is readily isolated by removing the reaction solvent, and further purification can be achieved if desired by normal means such as salt formation, crystallization, and chromatography.

The required starting material, i.e. the spiro amine, can be synthesized from readily available reactants, utilizing any of several methods:

-In one method, an N-protected form of a derivatized diethylamine is reacted with a bicyclic ketone according to scheme 2:

Scheme 2



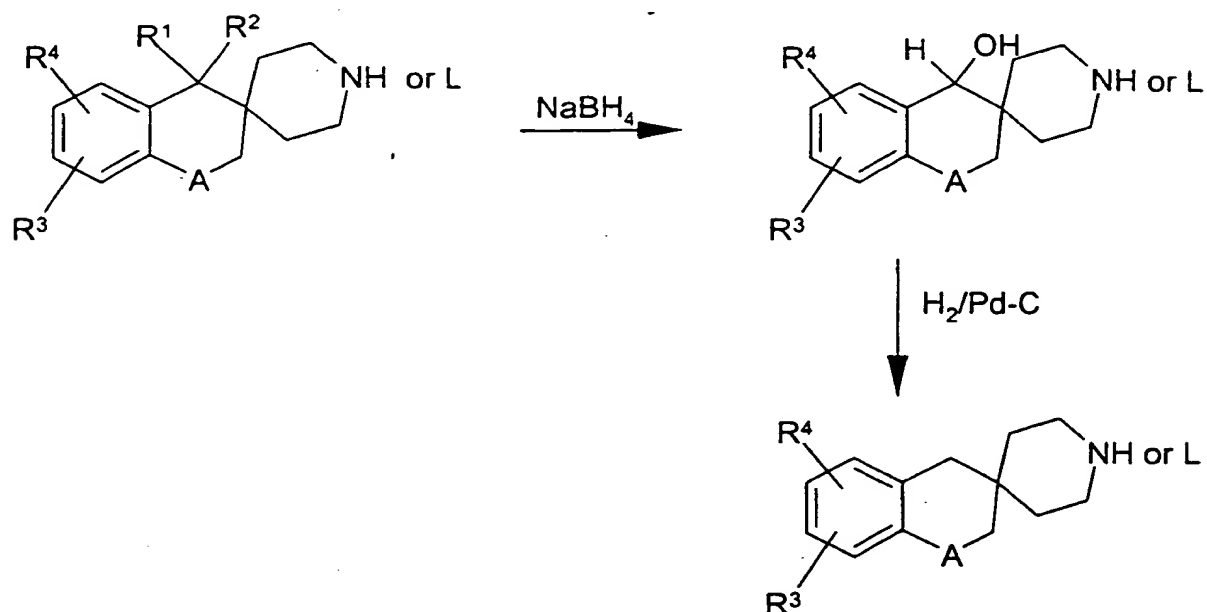
In the above scheme 2, P is an amine-protecting group that is easily removed, for example ethoxycarbonyl or benzyl. The protected diethylamine derivative is readily reacted with a bicyclic ketone in the presence of a strong base such as NaH. This reaction results in formation of the spiro amino derivative, which is readily de-protected by conventional means, for instance by reaction with hydrochloric acid.

Scheme 2 illustrates the preparation of keto substituted starting materials, i.e. where R^1 and R^2 together are oxo. Such compounds are easily converted to the corresponding alcohol (R^1 is H, R^2 is OH) by reaction with a reducing agent such as NaBH_4 , generally in a solvent such as methanol or ethanol.

-18-

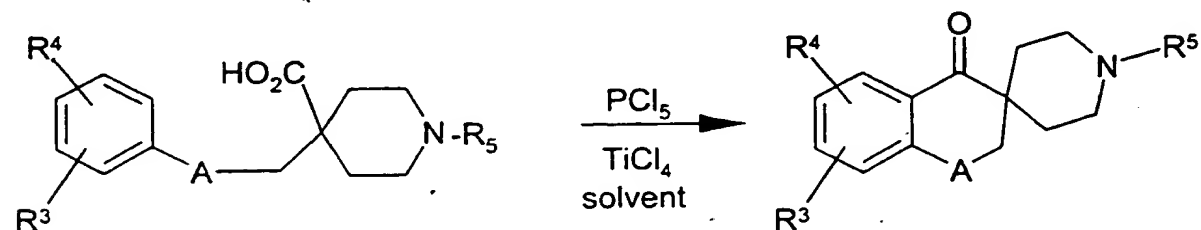
The alcohol can be further reduced by catalytic hydrogenation, for example by reaction with hydrogen gas in the presence of 10% palladium on carbon. These reactions are illustrated in Scheme 3 :

5

Scheme 3

The invention compounds of Formula I can alternatively be prepared by starting with a suitably substituted piperidine derivative, as shown in Scheme 4 :

10

Scheme 4

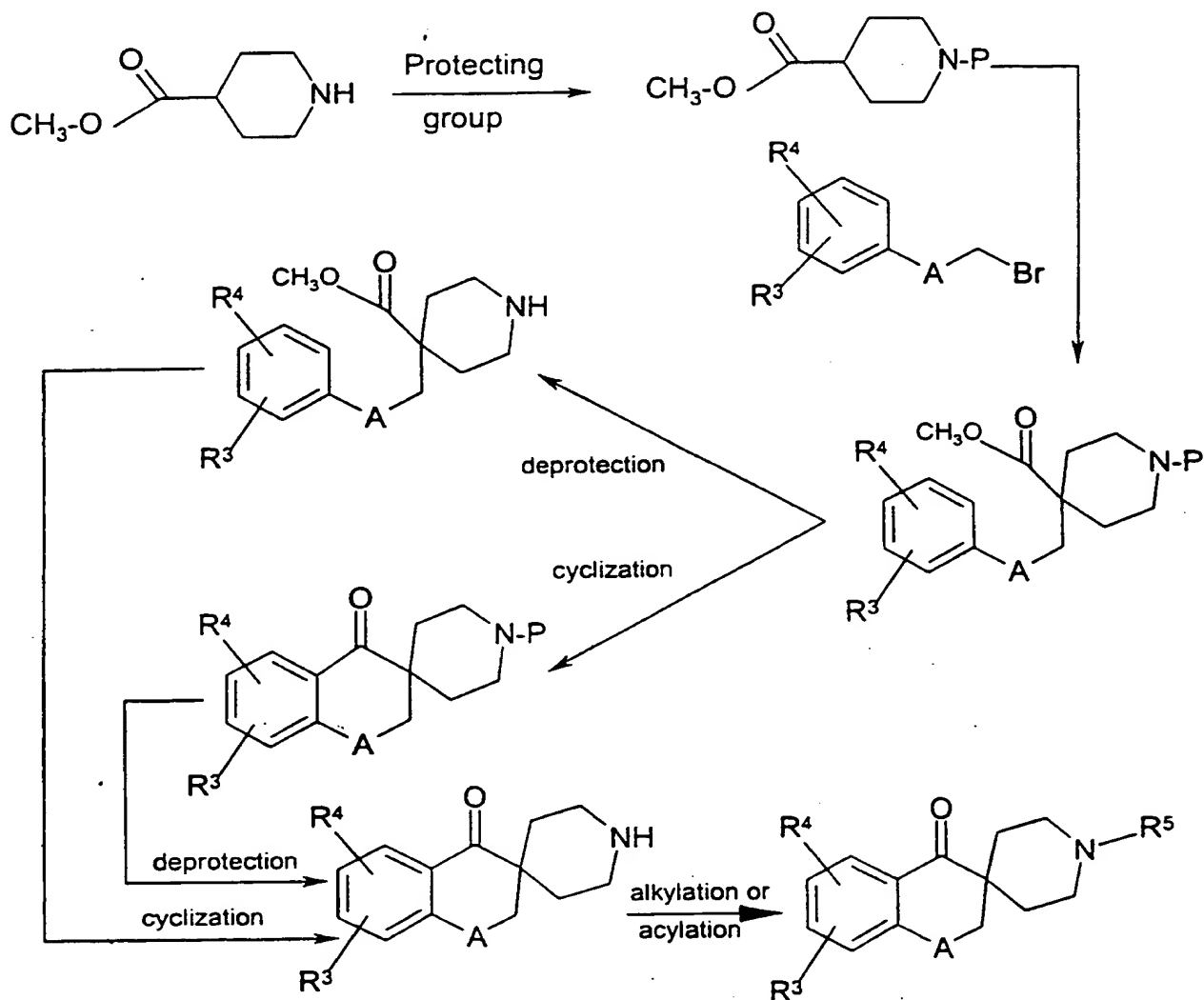
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The cyclization reaction is accomplished by reacting the substituted piperidine with strong dehydrating agents such as phosphorus pentachloride and titanium tetrachloride, generally in an unreactive organic solvent such as benzene, toluene, xylene, or chloroform. The reaction normally is complete within 2 h when carried out at a temperature of $30^\circ C$ to $60^\circ C$.

The cyclized product is a compound of Formula I wherein R^1 and R^2 together are oxo, which, as noted above in Scheme 3, can be reduced to the corresponding alcohol or alkane (R^1 and R^2 both hydrogen).

The substituted piperidine required for the above reaction is readily prepared as shown in Scheme 5:

Scheme 5



In Scheme 5, the methyl 4-piperidine formate is reacted with an amine-protecting agent (i.e. to insert P). Typical amine-protecting groups include *tert*-butoxy carbonyl, benzyl and trimethylsilyl. The protected piperidine derivative is next

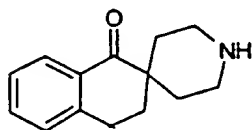
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reacted with a phenyl alkyl halide, for example phenylethyl bromide (where A is CH₂) or 2-phenylpropyl iodide (where A is CH-CH₃) or 3-phenylpropyl iodide (where A is CH₂ CH₂), in the presence of a strong base such as NaH or lithium diisopropylamide (LDA), generally in an unreactive solvent such as tetrahydrofuran, or benzene. The reaction, carried out at about -20°C, generally is substantially complete after about 2 - 4 h. The alkylated piperidine can then be deprotected (removal of the L-protecting group) and cyclized by reaction with PCl₅ and TiCl₄, or it can be cyclized first, and the L-protecting group subsequently removed.

The following detailed examples illustrate the synthesis of specific compounds provided by this invention. The examples are representative only, and are not intended to be limiting in any respect.

EXAMPLE 1

3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]

Stage 1: Bis(2-bromoethyl)amine hydrobromide.

157.5 g (1.5 mol) of diethanolamine and then, with stirring, 1.35 l of 48% HBr (exothermic reaction) are introduced into a 2 l three-necked flask which can be equipped either for reflux or for distillation. The solution is heated at a bath temperature of 180-200°C, in order to distill off a volume of 350 ml at a vapour temperature of 122°C. The device is adjusted to the reflux position and is maintained for 1 h. A further distillation is carried out as above, in order to collect a distillate of 465 ml. The device is again adjusted for reflux for 3.75 h and then 400 ml are distilled off. The mixture is cooled and 300 ml of ethyl acetate are added to the residue. The suspension is stirred for 1 h in an ice bath. The precipitate is filtered off and then washed with ethyl acetate. 367 g of a white crystalline product are obtained. Yd = 78.5%, M.p. (°C) = 130-135°C.

Stage 2: Ethyl bis(2-bromoethyl)carbamate.

367 g (1.17 mol) of the product obtained in the preceding stage and then 108 ml, i.e. 122.6 g (1.13 mol), of ethyl chloroformate are added, with stirring, to a 4 l reactor containing 1.8 l of a water/ice mixture. Approximately 1.3 l of a 2N sodium hydroxide solution are run into the solution over 5 min in order to achieve a continuing pH of 11, while maintaining a temperature below 5°C. The mixture is stirred for 5 min and then acidified to pH 1 with concentrated HCl. Extraction is carried out with 3 times 1 l of ethyl ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na₂SO₄. The solvent is evaporated. The residue is chromatographed by eluting with CH₂Cl₂. 208.5 g of product are obtained. Yd = 58%, TLC (CH₂Cl₂): R_f = 0.6, N.M.R.: CDCl₃ ¹H ((ppm): 1.2 (t, 3H), 3.4-3.55 (m, 4H), 3.6-3.7 (m, 4H), 4.1-4.2 (q, 2H)).

15

Stage 3: Ethyl 3,4-dihydro-1-oxospiro [naphthalene-2(1H),4'-piperidine]-1'-carboxylate.

69 g (0.472 mol) of 1-tetralone and 234 ml of DMF, dried beforehand over molecular sieve, are introduced into a reactor which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -15°C with a dry ice/acetone bath and 34.6 g (1.15 mol) of 80% sodium hydride, as a dispersion in mineral oil, are added thereto. The temperature is allowed to rise to approximately 20-25°C (exothermic reaction). The reaction mixture is stirred for 1.5 h at a temperature below 30°C.

25

At the same time, a solution of 208 g (0.69 mol) of ethyl bis(2-bromoethyl)carbamate in 234 ml of DMF (dried beforehand over molecular sieve) is cooled, in a reactor which is protected from moisture and which is under an inert atmosphere, to -25°C with a dry ice/acetone bath. The reaction liquors, prepared at the same time, are introduced by transfer under nitrogen and run in over 10 min at a temperature of -25°C. The temperature is allowed to rise (exothermic reaction with rise in the temperature to 45°C). The reaction mixture is then cooled in order to maintain it at approximately 30°C. It is subsequently

30

-22-

brought to 50°C for 2 h and then the solvent is evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 1.2 l of ice-cold water and extracted with 3 times 600 ml of ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na₂SO₄. After evaporating the solvent, a dark brown oily residue is obtained which is purified by fast chromatography by eluting with CH₂Cl₂ gradually enriched with acetone. 57.7 g (0.2 mol) of product are obtained (Yd = 42.5%), TLC (97/3 CH₂Cl₂/acetone): R_f = 0.45.

N.M.R.: CDCl₃ ¹H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.85-2.95 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

Stage 4: 3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine].

57.7 g (0.2 mol) of ethyl 3,4-dihydro-1-oxospiro-[naphthalene-2(1H),4'-piperidine]-1'-carboxylate and then 1.6 l of 6N HCl are introduced into a reactor. The mixture is stirred and brought to reflux for 14 h. It is then cooled and extracted with twice 500 ml of ethyl ether. The aqueous phase is basified while cold with NaOH and extracted with 3 times 500 ml of ethyl ether. The organic phase is washed and dried over Na₂SO₄. After evaporating the solvent, the residue is purified by chromatography by eluting with CH₂Cl₂ gradually enriched with methanol containing 10% NH₄OH.

Weight: 31 g, Yd = 72%, TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.2-0.35.

N.M.R.: CDCl₃ ¹H ((ppm) Base: 1.35-1.45 (m, 2H), 1.8-1.9 (m, 2H), 2.0 (t, 2H), 2.1 (s, 1H), 2.75-2.85 (m, 2H), 2.85-3.0 (m, 4H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the product in CH₂Cl₂. The mixture is concentrated to dryness and then the product is crystallized from a methanol/ether mixture.

White powder, M.p. = 235°C, TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.35.

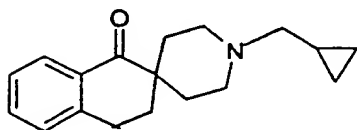
Analysis conforms to C₁₄H₁₈ClNO.

IR: 2995, 2700, 1675, 1600, 1440, 1395, 1210, 1090, 990, 750, 740 cm⁻¹

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EXAMPLE 2

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



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10 g (46.4 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine] and then 80 ml of DMF and 36.2 ml of THF are introduced into a three-necked flask. 6.89 g (51 mmol) of (bromomethyl)cyclopropane and 7.8 g (92.8 mmol) of NaHCO₃ are added. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 200 ml of water and extracted with 3 times 100 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 100 ml of ether. The organic phase is washed with an NaCl solution and dried over Na₂SO₄. Once the solvent has been evaporated, 12 g of an oily residue are obtained. The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH₂Cl₂. The mixture is concentrated to dryness and then the product is crystallized by addition of 20 ml of ether to a methanolic solution of the product, crystallization is allowed to take place overnight at 20-25°C and then the product is filtered off and washed with water. After drying, 8.4 g of product are obtained.

White powder, M.p. = 243°C, TLC (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.55.

Analysis conforms to C₁₈H₂₄ClNO.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.4-0.55 (m, 2H), 0.75-0.8 (m, 2H), 1.3-1.4 (m, 1H), 2.1-2.2 (m, 4H), 2.4-2.55 (m, 2H), 2.85-2.9 (m, 2H), 3.0-3.05 (m, 2H), 3.2-

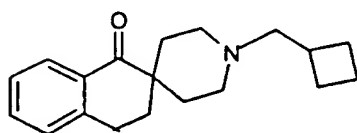
3.3 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.25 (m, 1H), 7.3-7.35 (m, 1H), 7.5-7.6 (m, 1H),
7.95-8.0 (m, 1H), 12.0-12.2 (m, 1H).

IR: 2990, 2700, 1675, 1600, 1420, 1395, 1320, 1080, 980, 900, 760, 740 cm^{-1}

5 The corresponding iodomethylate was also obtained. MP: 162°C

EXAMPLE 3

1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



10 The method described for Example 2, using cyclobutylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 235°C.

TLC: (92/8 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ containing 10% NH_4OH): $R_f = 0.7$. Analysis conforms to $\text{C}_{19}\text{H}_{26}\text{ClNO}$.

15 N.M.R.: CDCl_3 ^1H ((ppm) HCl: 1.8-2.25 (m, 10H), 2.4-2.5 (m, 2H), 2.95-3.1 (m, 5H), 3.1-3.25 (m, 2H), 3.25-3.35 (m, 2H), 7.2-7.35 (m, 2H), 7.45-7.55 (m, 1H), 7.9-8.0 (m, 1H), 11.95-12.15 (m, 1H))

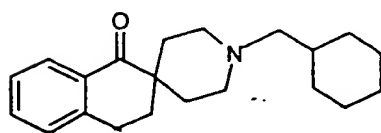
IR: 3400, 2900, 2650, 2500, 1680, 1590, 1430, 1360, 1300, 1220, 1140, 1100, 1040, 960, 930, 900, 800, 770, 740, 640 cm^{-1}

20

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EXAMPLE 4

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



-25-

The method described for Example 2, using cyclohexylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 265°C.

TLC: (93/7 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.8. Analysis conforms to C₂₁H₃₀ClNO.

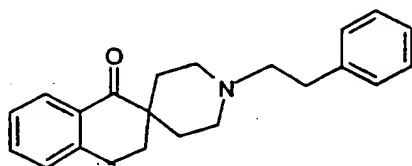
5 N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.95-1.3 (m, 5H), 1.6-2.1 (m, 10H), 2.5-2.65 (m, 2H), 2.7-2.8 (m, 2H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 2H), 3.3-3.4 (m, 2H), 7.15-7.3 (m, 2H), 7.4-7.5 (m, 1H), 7.9-7.95 (m, 1H), 11.6-11.8 (m, 1H))

IR: 3400, 2900, 2500, 1680, 1600, 1440, 1360, 1300, 1220, 1150, 1110, 1060, 980, 910, 760, 735 cm⁻¹

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EXAMPLE 5

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



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The method described for Example 2, using phenethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = >275°C, Yd = 55%.

TLC: (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.85. Analysis conforms to C₂₂H₂₆ClNO.

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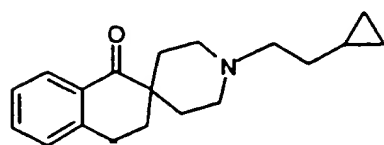
N.M.R.: CDCl₃ ¹H ((ppm) HCl: 2.0-2.15 (m, 4H), 2.3-2.45 (m, 2H), 2.9-3.0 (m, 2H), 3.05-3.25 (m, 6H), 3.4-3.5 (m, 2H), 7.1-7.3 (m, 7H), 7.4-7.45 (m, 1H), 7.85-7.9 (m, 1H), 12.25-12.45 (m, 1H))

IR: 3400, 2900, 2500, 1670, 1600, 1450, 1360, 1290, 1220, 1110, 1010, 960, 820, 800, 740, 700 cm⁻¹

EXAMPLE 6

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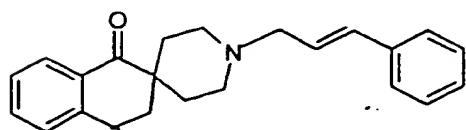
1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



-26-

0.94 g (4.36 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] and then 10 ml of DMF are introduced into a three-necked flask. 1.3 g (8.7 mmol) of (bromoethyl)cyclopropane in 2 ml of DMF and then 0.73 g (8.7 mmol) of NaHCO₃ are added to the solution obtained. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are removed at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 50 ml of water and extracted with three times 50 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 50 ml of ether. The organic phase is washed with an NaCl solution and dried over Na₂SO₄. The solvent is removed. The oily residue is purified by fast chromatography by eluting with CH₂Cl₂ enriched with methanol. 0.6 g is obtained, the hydrochloride of which is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH₂Cl₂. The mixture is concentrated to dryness and then the product is crystallized by addition of 30 ml of ether to a solution of the product in 5 ml of isopropanol. Crystallization is allowed to take place for 14 h at 20-25°C and then the product is filtered off and washed with ether. After drying, 0.5 g of white powder is obtained, M.p. = 244°C, TLC: (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.35. Analysis conforms to C₁₉H₂₆ClNO. N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.1-0.3 (m, 2H), 0.45-0.65 (m, 2H), 0.7-0.8 (m, 1H), 1.6-2.6 (m, 8H), 2.9-3.5 (m, 8H), 7.2-7.4 (m, 2H), 7.4-7.6 (t, 1H), 7.9-8.05 (d, 1H), 12.15 (1H)) IR: 2900, 2450, 1670, 1600, 1430, 1290, 1220, 950, 890, 740 cm⁻¹

EXAMPLE 7

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

-27-

Prepared according to the method described in Example 2 with cinnamyl bromide, then purification by chromatography and crystallization of the hydrochloride.

White powder, M.p. = 228°C.

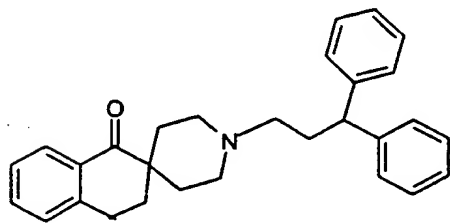
TLC: (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.55. Analysis conforms to C₂₃H₂₆ClNO.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 2.0-2.25 (m, 4H), 2.3-2.5 (m, 2H), 2.9-3.85 (m, 8H), 6.4-6.6 (m, 1H), 6.6-6.8 (d, 1H), 7.1-7.6 (m, 8H), 7.9-8.0 (d, 1H), 12.1 (1H))

IR: 2900, 2400, 1670, 1590, 1420, 1290, 1220, 970, 730, 690 cm⁻¹

EXAMPLE 8

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



Prepared according to the method described in Example 6 with 3,3-diphenylpropyl bromide and preparation of the hydrochloride. A white powder is obtained, M.p. =

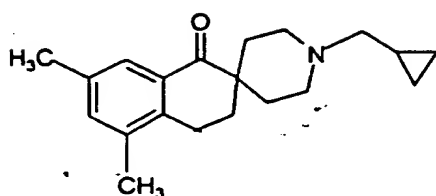
257°C, TLC (95/5 CH₂Cl₂/MeOH): R_f = 0.35. Analysis conforms to C₂₉H₃₂ClNO.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 2.0-2.2 (m, 4H), 2.4-3.5 (m, 12H), 3.9-4.05 (m, 1H), 7.2-7.4 (m, 12H), 7.4-7.6 (m, 1H), 7.9-8.0 (m, 1H), 12.3 (1H))

IR: 2900, 2350, 1670, 1590, 1450, 1300, 1220, 910, 740, 700 cm⁻¹

EXAMPLE 9

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1H),4'-piperidine]



3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1H),4'-piperidine] is prepared according to the methods described for the synthesis of Example 1. The "N" alkylation is identical to that described in Example 6. The hydrochloride is obtained in the form of a white powder, M.p. > 260°C.

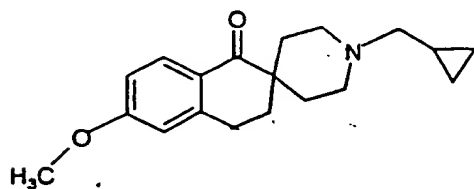
TLC: (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.5. Analysis conforms to C₂₀H₂₈ClNO.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.3-0.4 (m, 2H), 0.7-0.8 (m, 2H), 1.1-1.3 (m, 1H), 2.0-2.1 (m, 4H), 2.2 (s, 3H), 2.3 (s, 3H), 2.35-2.45 (m, 2H), 2.7-2.85 (m, 4H), 3.0-3.2 (m, 2H), 3.4-3.5 (m, 2H), 7.15 (s, 1H), 7.6 (s, 1H), 12.15 (1H))

IR: 3400, 2900, 2500, 1670, 1605, 1470, 1430, 1280, 1180, 1020, 970, 950, 880, 830 cm⁻¹

EXAMPLE 10

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]



By the process of Example 9, the hydrochloride is obtained.

White powder, M.p. > 255°C.

TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.35.

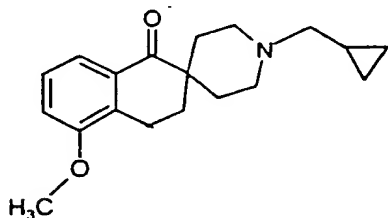
Analysis conforms to C₁₉H₂₆ClNO₂.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-2.95 (m, 2H), 2.95-3.05 (m, 2H), 3.2-3.4 (m, 2H), 3.45-3.6 (m, 2H), 3.85 (s, 3H), 6.7 (s, 1H), 6.85 (d, 1H), 7.9-8.0 (d, 1H), 12.15 (1H))

IR: 2900, 2420, 1660, 1590, 1430, 1250, 1220, 960, 830, 600 cm⁻¹

EXAMPLE 11

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]



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Same process as for Example 10; the hydrochloride is obtained.

White powder, M.p. = 244°C.

TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.75.

Analysis conforms to C₁₉H₂₆ClNO₂.

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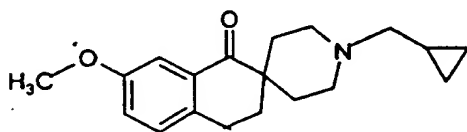
N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.1-3.3 (m, 2H), 3.5-3.6 (m, 2H), 3.85 (s, 3H), 7.0-7.1 (m, 1H), 7.25-7.35 (m, 1H), 7.5-7.6 (m, 1H), 12.1-12.2 (1H))

IR: 2930, 2560, 2360, 1680, 1580, 1470, 1435, 1260, 1060, 970, 750 cm⁻¹

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EXAMPLE 12

1'-(methylcyclo-propyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]



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By using the same methods as for Example 10, the hydrochloride is obtained.

White powder, M.p. = 235°C.

TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.70-0.75.

Analysis conforms to C₁₉H₂₆ClNO₂.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.2-3.3 (m, 2H), 3.5-3.6

25

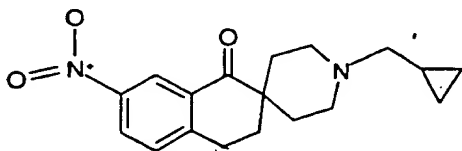
(m, 2H), 3.80 (s, 3H), 7.0-7.1 (m, 1H), 7.15-7.25 (m, 1H), 7.4 (s, 1H), 12.1-12.2 (1H))

IR: 2930, 2510, 2445, 1670, 1610, 1495, 1415, 1250, 1025 cm^{-1}

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EXAMPLE 13

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1H),4'-piperidine]



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Stage 1: 2.4 g (8.35 mmol) of ethyl 3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine]-1'-carboxylate, prepared according to the method described in Stage 3 of Example 1, and 35 ml of concentrated sulphuric acid are introduced into a three-necked flask. 0.79 g (12.5 mmol) of fuming nitric acid is added to the solution cooled to 0°C. The mixture is stirred for 1 h at 0°C and then for 2 h at 20-25°C. The solution is precipitated from 100 ml of water and ice and then extracted with three times 100 ml of CH_2Cl_2 . The organic phase is washed successively with water and saturated NaCl solution. After drying over Na_2SO_4 and evaporating the solvent, 2.75 g of an oil are obtained, which oil is chromatographed by eluting with CH_2Cl_2 gradually enriched with acetone. 1.5 g of ethyl 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1H), 4'-piperidine]-1'-carboxylate are obtained in the form of an oily residue which crystallizes. Yd = 54%, TLC (98/2 CH_2Cl_2 /acetone): R_f = 0.3.

N.M.R.: CDCl_3 ^1H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.9-3.0 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.3 (d, 1H), 8.2 (d, 1H), 8.8 (s, 1H))

25

Stage 2: 1.5 g of the product of the preceding stage is hydrolysed by the process described in Stage 4, Example 1. After chromatography by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH , 0.45 g is isolated. TLC (90/10 CH_2Cl_2 /MeOH containing 10% NH_4OH): R_f = 0.1.

-31-

Stage 3: 0.22 g (0.845 mmol) of 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] obtained in the preceding stage is suspended in 3 ml of acetonitrile. A solution of 0.343 g (2.54 mmol) of cyclopropylmethyl bromide in 0.5 ml of acetonitrile is added with stirring. The reaction mixture is brought to reflux and maintained for approximately 5 h.

The solvent is removed and the residue is taken up in 20 ml of CH₂Cl₂ and extracted with 20 ml of N/1 HCl. The acidic phase is basified while cold with a dilute sodium hydroxide solution to pH 12 and extracted with 3 times 20 ml of CH₂Cl₂. After washing, drying and removing the solvent, the residue is chromatographed by eluting with CH₂Cl₂ gradually enriched with methanol containing 10% NH₄OH. 0.130 g of 3,4-dihydro-1'-(cyclopropylmethyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] is obtained. TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.7.

The hydrochloride is prepared as described above. White powder, M.p. = 256°C.

TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.7.

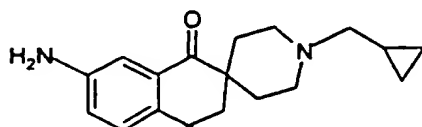
Analysis conforms to C₁₈H₂₃ClN₂O₃.

N.M.R.: CDCl₃ ¹H (ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.4 (m, 1H), 2-2.25 (m, 4H), 2.4-2.6 (m, 2H), 2.8-2.9 (m, 2H), 3.05-3.3 (m, 4H), 4.5-4.6 (m, 2H), 7.45 (d, 1H), 8.3 (d, 1H), 8.8 (s, 1H), 12.1 (1H)

IR: 2940, 2500, 2440, 1690, 1610, 1520, 1410, 1345, 1220, 1105, 960 cm⁻¹

EXAMPLE 14

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



-32-

60 mg (0.19 mmol) of 3,4-dihydro-1'-(methylcyclo-propyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine], obtained as described in Example 13, are dissolved in 1 ml of THF and then, with stirring, 0.21 g of tin chloride hydrate is introduced. The solution is brought to reflux for 1 h. The reaction liquors are charged to a saturated NaHCO₃ solution and extracted with 3 times CH₂Cl₂. The organic phase is washed and dried over Na₂SO₄. The solvent is evaporated and the residue obtained is chromatographed by eluting with CH₂Cl₂ gradually enriched with methanol containing 10% NH₄OH. 29 mg of product are obtained.

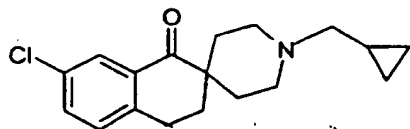
N.M.R.: CDCl₃ ¹H ((ppm): 0.1-0.2 (m, 2H), 0.4-0.55 (m, 2H), 0.85-1.0 (m, 1H), 1.6-1.7 (m, 2H), 1.9-2.1 (m, 4H), 2.3-2.4 (m, 2H), 2.5-2.75 (m, 4H), 2.8-2.9 (m, 2H), 3.6-3.8 (2H), 6.8 (d, 1H), 7.0 (d, 1H), 7.2 (s, 1H))

The hydrochloride is crystallized from ether. 26 mg of a yellow powder are obtained.

M.p. = 200°C, decomposition. TLC (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.45.

EXAMPLE 15

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: Piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester.

60 g (0.381 mol) of ethyl isonipecotate and 400 ml of THF are placed in a three-necked flask which is protected from moisture and which is under an inert atmosphere, and 18.3 g (0.458 mol) of sodium hydroxide pellets are added. A solution of 100 g (0.458 mol) of di-*t*-butyl dicarbonate in 170 ml of THF is added over 1 h with stirring to the suspension. The temperature reaches 45°C. The reaction mixture is left stirring for 14 h at 20-25°C and is then poured onto 2 l of water and ice and extracted with 3 times 500 ml of ether. The organic phase is washed with 3 times 250 ml of a saturated NaCl solution, dried over Na₂SO₄ and concentrated. The residue is chromatographed by eluting with CH₂Cl₂ gradually

-33-

enriched with acetone and then distilled under a vacuum of 0.09 mm Hg and at a vapour temperature of 95-102°C. 82 g are obtained (Yd = 83.6%). TLC (95/5 CH₂Cl₂/acetone): R_f = 0.60.

5 N.M.R.: CDCl₃ ¹H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.5-1.6 (m, 2H), 1.8-1.9 (m, 2H), 2.35-2.45 (m, 1H), 2.7-2.85 (m, 2H), 3.9-4.0 (m, 2H), 4.05-4.15 (q, 2H))

Stage 2: 4-(4-Chlorophenethyl)piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester

10 6.16 g (60.9 mmol) of diisopropylamine and 174 ml of THF, dried over molecular sieve, are introduced, by transfer under nitrogen, into a three-necked flask which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -10°C and 24.3 ml of 2.5N *n*-butyllithium in hexane (60.9 mmol) are run in. The mixture is stirred for 15 min at -10°C and cooled to -70°C, and a solution of 10.4 g (40.6 mmol) of the product from the preceding Stage 1 in 86 ml of THF
15 is run in over approximately 20 min. The mixture is stirred for 10 min at -70°C and then 10.9 g (60.9 mmol) of HMPT are added. The mixture is kept stirring at -70°C for 1.5 h and a solution of 4-chlorophenethyl bromide (10.7 g, 48.7 mmol) in 86 ml of THF is run in over 20 min at -70°C. The mixture is stirred at 20-25°C for 14 h and then poured over 350 ml of water and extracted 3 times with ether.
20 The organic phase is washed with an N/1 HCl solution and then with a saturated NaCl solution. After drying and concentrating, 17 g of an orange oil are obtained, which oil is chromatographed by eluting with CH₂Cl₂ gradually enriched with hexane, and then with acetone. 11.8 g are obtained (Yd = 80%). TLC (95/5 CH₂Cl₂/acetone): R_f = 0.70.

25 NMR: CDCl₃ ¹H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.0-2.1 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.9 (m, 2H), 3.7-3.9 (m, 2H), 4.05-4.15 (q, 2H), 6.9-7.0 (m, 2H), 7.1-7.2 (m, 2H))

Stage 3: Ethyl 4-(4-chlorophenethyl)piperidine-4-carboxylate

30 10.8 g of the product from the preceding Stage 2 and 50 ml of CH₂Cl₂ are introduced into a three-necked flask which is protected from moisture. The solution is stirred and 25 ml of trifluoroacetic acid are added at 20-25°C. The mixture is kept stirring for 30 min and then concentrated to dryness and the

residue is taken up in ether. The organic phase is washed with a 10% sodium hydroxide solution and then with a saturated NaCl solution. After drying and concentrating, 9 g of an oil are obtained, which oil crystallizes.

TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.45.

5 NMR: CDCl₃ ¹H ((ppm): 1.1-1.25 (t, 3H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.1-2.2 (m, 2H), 2.35-2.45 (m, 2H), 2.6-2.7 (m, 2H), 2.9-3.0 (m, 2H), 3.3 (1H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

10 Stage 4: Ethyl 1-(cyclopropylmethyl)-4-(4-chlorophenethyl)piperidine-4-carboxylate

3.4 g (11.5 mmol) of the product from the preceding Stage 3, 85 ml of THF, dried over molecular sieve, and then, with stirring, 14.9 ml of triethylamine and 2.4 ml (20.9 mmol) of 85% (bromomethyl)cyclopropane are successively introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. The mixture is brought to reflux for 14 h and then concentrated to dryness, and the residue is taken up in water and extracted twice with ether. The organic phase, washed with a saturated NaCl solution and dried, is concentrated. 3 g of crude product are obtained, which product is chromatographed (eluent: CH₂Cl₂ gradually enriched with methanol containing 10% NH₄OH). 2.6 g of oily product are obtained. Yd = 65%.

20 TLC (95/5 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.50.

N.M.R.: CDCl₃ ¹H ((ppm): 0.0-0.1 (m, 2H), 0.35-0.45 (m, 2H), 0.7-0.8 (m, 1H), 1.1-1.2 (t, 3H), 1.4-1.5 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.1 (m, 2H), 2.1-2.2 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.85 (m, 2H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

25 Stage 5: 1-(Cyclopropylmethyl)-4-(4-chlorophenethyl)-piperidine-4-carboxylic acid

2.2 g (6.28 mmol) of the preceding ester and 6.6 ml of anhydrous dimethyl sulphoxide are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. A solution of potassium *t*-butoxide (4.4 g, 39 mmol) in 30 ml of dimethyl sulphoxide is added with stirring. The mixture is

-35-

left stirring for 2 h at 20-25°C. The reaction mixture is charged to 200 ml of water and then washed with ether. The aqueous phase is acidified to pH 5-7 with 10% HCl. The precipitate is filtered off and washed with water. The acid obtained is crystallized from a CH₂Cl₂/methanol mixture. M.p. = 250°C.

5 NMR: CDCl₃ ¹H ((ppm): 0.2-0.3 (m, 2H), 0.5-0.6 (m, 2H), 1.07-1.1 (m, 1H), 1.6-1.9 (m, 4H), 2.25-2.35 (m, 2H), 2.5-2.6 (m, 2H), 2.65-2.75 (m, 2H), 2.8-2.9 (m, 2H), 3.3-3.4 (m, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))
IR: 3370, 1490, 1445, 1380, 1240, 1170, 1095, 965, 805 cm⁻¹.

10 Stage 6: 7-Chloro-3,4-dihydro-1'-(cyclopropylmethyl)-1-oxospiro[naphthalene-2(1H),4'-piperidine].

0.3 g (0.9 mmol) of the acid obtained previously and 6 ml of benzene are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. 0.24 g of PCl₅ and 6 ml of CH₂Cl₂ are added, followed by
15 a further 0.24 g of PCl₅. The mixture is stirred for 2 h at 20-25°C. The mixture is cooled to 0°C, 0.44 ml of tin tetrachloride is introduced (copious precipitation), 12 ml of CH₂Cl₂ are added and the mixture is maintained at 0°C for 1 h and then at 20-25°C for 14 h. The solvents are removed and the residue is taken up in water. The aqueous phase is washed with ether and then basified to pH 12 with
20 NaOH and extracted with ether. The organic phase is washed, dried and concentrated. The crude product is chromatographed by eluting with CH₂Cl₂ gradually enriched with methanol containing 10% NH₄OH. 22 mg of product are obtained, which product is treated in solution in CH₂Cl₂ with 5N ethereal hydrochloric acid. After crystallization from ethyl acetate, the product is filtered
25 off and dried at 50°C under vacuum.

White powder. TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.55.
M.p. = 263°C.

N.M.R.: CDCl₃ ¹H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.3 (m, 1H), 2.0-2.15 (m, 4H), 2.4-2.55 (m, 2H), 2.8-2.9 (m, 2H), 2.95-3.05 (m, 2H), 3.1-3.3
30 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.3 (m, 1H), 7.4-7.5 (m, 1H), 7.9 (s, 1H), 12.2 (1H))

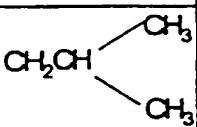
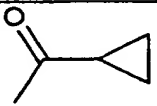
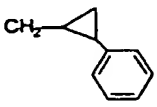
IR: 2930, 2440, 1720, 1490, 1230, 1185, 1095, 1025, 810 cm⁻¹.

EXAMPLES 16-34

Following the general procedures described above, the following additional compounds listed in table 1 were prepared.

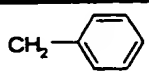
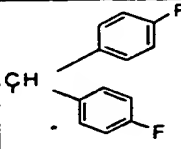
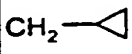
5

Table 1











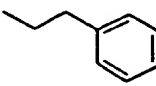
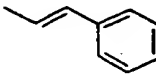
Example	R ¹	R ²	R ³	R ⁴	A	R ⁵
16	=O		H	H	CH ₂	CH ₃
17	=O		H	H	CH ₂	CH ₂ CH=CH ₂
18	=O		H	H	CH ₂	
19	=O		H	H	CH ₂	
20	=O		H	H	CH ₂	

10

Table 1 (cont.)

Example	R ¹	R ²	R ³	R ⁴	A	R ⁵
21	=O		H	H	CH ₂	
22	=O		H	H	CH ₂	
23	H	OH	H	H	CH ₂	

-37-

24	H	H	H	H	CH ₂	CH ₂ — 
25	=O		H	H	Bond	CH ₂ — 
26	=O		H	H	CH ₂ CH ₂	CH ₂ — 
27	=O		H	H		CH ₂ — 
28	=O		6-Cl	H	CH ₂	CH ₂ — 
29	=O		6-F	H	CH ₂	CH ₂ — 
30	=O		6:OCH ₃	7:OCH ₃	CH ₂	CH ₂ — 
31	=O		H	H	CH ₂	
32	=O		H	H	CH ₂	
33	=O		H	H	CH ₂	
34	=O		6:OCH ₃	H	CH ₂	

MP and NMR data for the compounds of examples 16 to 34 are provided below:

5

Example 16

MP = 240-243°C

R.M.N. CDCl₃ ¹H δ (ppm) Base: 1,5-1,6 (m, 2H); 1,95-2,05 (m, 4H); 2,25 (s, 3H); 2,3-2,4 (m, 2H); 2,45-2,55 (m, 2H); 2,9-2,95 (m, 2H); 7,1-7,15 (m, 1H); 7,2 - 7,25 (m, 1H); 7,35-7,4 (m, 1H); 7,9-7,95 (m, 1H)

10

Example 17

MP = 242-244°C

-38-

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 2,05-2,15 (m,4H); 2,3-2,45 (m,2H); 3,0-3,1 (m,2H); 3,1-3,25 (m,2H); 3,35-3,5 (m,2H); 3,55-3,6 (m,2H); 5,4-5,55 (m,2H); 6,1-6,25 (m,1H); 7,2-7,35 (m,2H); 7,45-7,5 (m,1H); 7,9-7,95 (m,1H); 12,3-12,45 (m,1H)

5

Example 18

MP = 244-245°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 1,15 (d,6H); 2,0-2,1 (m,4H); 2,15-2,3 (m,1H); 2,55-2,65 (m,2H); 2,75-2,8 (m,2H); 2,95-3,0 (m,2H); 3,1-3,25 (m,2H); 3,35-3,45 (m,2H); 7,2-7,35 (m,2H); 7,45-7,5 (m,1H); 7,9-7,95 (m,1H); 11,7-11,8 (m,1H)

10

Example 19

MP = 95-97°C

R.M.N. CDCl_3 ^1H δ (ppm) base: 0,6-0,7 (m,2H); 0,8-0,95 (m,2H); 1,4-1,5 (m,2H); 1,6-1,7 (m,1H); 1,8-2,1 (m,4H); 2,9-3,5 (m,2H); 3,4-3,8 (m,4H); 7,1-7,3 (m,2H); 7,35-7,45 (m,1H); 7,9-8,0 (m,1H);

15

Example 20

MP = 220-221°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 1,05-1,3 (m,2H); 1,5-1,9 (m,1H); 2,0-2,2 (m,5H); 2,3-2,55 (m,2H); 2,9-3,4 (m,6H); 3,4-3,6 (m,2H); 7,0-7,6 (m,8H); 7,9-8,1 (m,1H); 12,2-12,4 (m,1H)

20

Example 21

MP = 261-262°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 2,0-2,1 (m,4H); 2,4-2,5 (m,2H); 2,95-3,05 (m,2H); 3,1-3,25 (m,2H); 3,3-3,4 (m,2H); 4,1-4,15 (m,2H); 7,2-7,35 (m,2H); 7,4-7,5 (m,4H); 7,65-7,7 (m,2H); 7,9-7,95 (m,1H); 12,25-12,5 (m,1H)

25

30

Example 22

MP = > 250°C

R.M.N. CDCl_3 ^1H δ (ppm) base: 1,4-1,55 (m,2H); 1,9-2,05 (m,4H); 2,2-2,35 (m,2H); 2,4-2,55 (m,2H); 2,8-2,95 (m,2H); 4,2 (s,1H); 6,8-7,0 (m,4H); 7,15 (d,1H); 7,2-7,35 (m,5H); 7,4 (t,1H); 7,9 (d ,1H)

5

Example 23

MP = 91-93°C

R.M.N. CDCl_3 ^1H δ (ppm) base: -0,05-0,05 (m,2H); 0,35-0,45 (m,2H); 0,7-0,85 (m,1H); 1,25-1,85 (m,7H); 2,2 (d,2H); 2,2-2,4 (m,2H); 2,5-2,6 (m,1H); 2,6-2,7 (m,3H); 4,2 (s,1H); 7,0- 7,3 (m ,4H)

10

Example 24

MP = 256-258°C

R.M.N. CDCl_3 ^1H δ (ppm) base: 0,0-0,1 (m,2H); 0,4-0,5 (m,2H); 0,75-0,85 (m,1H); 1,45-1,55 (m,4H); 1,6-1,65 (m,2H); 2,2 (d,2H); 2,35-2,6 (m,6H); 2,7-2,8 (m,2H); 6,9- 7,05 (m ,4H)

15

Example 25

MP = 241°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,0-0,15 (m,2H); 0,4-0,55 (m,2H); 0,75-0,9 (m,1H); 1,35 (d,2H); 1,9-2,15 (m,4H); 2,25 (d,2H); 2,9 (s,2H); 3,0 (d,2H); 7,25 (t,1H); 7,35 (d 1H); 7,5 (t,1H); 7,65 (d,1H); 12,1-12,2 (1H)

20

Example 26

MP = 242-243°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,7-0,8 (m,2H); 1,2-1,35 (m,1H); 1,85-2,0 (m,4H); 2,2-2,3 (m,2H); 2,3-2,4 (m,2H); 2,7-2,9 (m,6H); 3,4-3,5 (m,2H); 7,15-7,4 (m,4H); 12,1-12,3 (1H)

25

Example 27

MP = 234°C

30

-40-

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 1,4(dd,3H); 1,85 (m,2H); 2,1 (m,3H); 2,3 (m,1H); 2,75 (m,2H); 2,9 (m, 2H) 3,25 (m,1H); 3,45-3,8 (m,3H); 7,3-7,45 (m,2H); 7,6 (m,1H); 8,0 (dd,1H); 12,1 (1H)

5 **Example 28**

MP = > 250°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,1-2,2 (m,4H); 2,4-2,55 (m,2H); 2,9-2,95 (m,2H); 3,0-3,05 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 7,25-7,3 (m,2H); 7,9,7,95 (m,1H); 12,2 (1H)

10

Example 29

MP = 227°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,0-2,2 (m,4H); 2,4-2,6 (m,2H); 2,85-2,95 (m,2H); 3,0-3,1 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 6,9-7,0 (m,1H); 7,0-7,1 (m,1H); 7,95-8,05 (m,1H); 12,1 (1H)

15

Example 30

MP = 229°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 2,15 (m,4H); 2,45 (td,2H); 2,9 (m,2H); 2,95 (m, 2H); 3,3 (m,2H); 3,55 (m,2H); 4,85 (s,3H); 4,95 (s,3H); 6,65 (s,1H); 7,45 (s,1H); 12,05 (1H)

20

Example 31

M P = 189-192°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 0,2-0,3 (m,1H); 0,6-0,7 (m,1H); 0,7-0,8 (m,1H); 0,8-0,9 (m,1H); 1,1-1,2 (m,1H); 1,55 (d,3H); 1,6-1,7 (m,1H); 2,1-2,2 (m,4H); 2,5-2,7 (m,2H); 3,0-3,1 (m,2H); 3,3-3,6 (m,4H); 7,2-7,25 (m,1H); 7,3-7,35 (m,1H); 7,45-7,5 (m1H); 8,0-8,05 (m,1H); 11,85 (1H)

30

Example 32

-41-

M P = > 235°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 1,7 (d,3H); 2,1-2,2 (m,4H); 2,4-2,5 (m,2H);
 2,6-2,7 (m,2H); 2,9-3,1 (m,4H); 3,2-3,3 (m,2H); 3,4-3,5 (m,2H); 5,3-5,4 (m,1H);
 5,6-5,7 (m,1H); 7,2-7,3 (m,1H); 7,3-7,35 (m,1H); 7,5-7,6 (m,1H); 7,95-8,0
 (m,1H); 12,2 (1H)

Example 33

M P = 209°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 2,1 (m,4H); 2,25 (m,2H); 2,45 (m,2H); 2,7
 (m,2H); 2,9 (m, 2H); 3,0 (m,2H); 3,15 (m,2H); 3,4 (m,2H); 7,1-7,35 (m,7H);
 7,5 (m,1H); 7,95 (m,1H); 11,95 (1H)

Example 34

M P = 228°C

R.M.N. CDCl_3 ^1H δ (ppm) HCl: 2,0-2,2 (m,4H); 2,4 (td,2H); 3,0 (m,2H); 3,3
 (qd, 2H); 3,45 (m,2H); 3,75 (t,2H); 3,85 (s,3H); 6,55 (qt,1H); 6,7 (m,2H);
 6,85 (dd,1H); 7,35 (m,3H); 7,45 (d,2H); 7,95 (d,1H); 11,95 (1H).

EXAMPLES 35-69

Following procedures known in the art, some of the tetralones described above
 were alkylated to yield the following additional compounds listed in table 2.

Table 2

Ex.	R ¹ -R ²	R ₃	R ₄	R ₅	A	R _f
35	=O	5:OCH ₃	H	(CH ₂) ₂ -c-C ₃ H ₅	CH ₂	0.7
36	=O	5:OCH ₃	H	CH ₂ -c-C ₄ H ₇	CH ₂	0.5
37	=O	5:OCH ₃	H	CH ₂ -c-C ₆ H ₁₁	CH ₂	0.8
38	=O	5:OCH ₃	H	CH ₂ -CH=CH-C ₆ H ₆	CH ₂	0.7
39	=O	5:OCH ₃	H	CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.7

-42-

40	=O	5:OCH ₃	H	CH ₂ -CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.55
41	=O	5:OCH ₃	H	(CH ₂) ₂ -CH-(C ₆ H ₆) ₂	CH ₂	0.90
42	=O	6:OCH ₃	H	(CH ₂) ₂ -c-C ₃ H ₅	CH ₂	0.4
43	=O	6:OCH ₃	H	CH ₂ -c-C ₄ H ₇	CH ₂	0.3
44	=O	6:OCH ₃	H	CH ₂ -c-C ₆ H ₁₁	CH ₂	0.55
45	=O	6:OCH ₃	H	CH ₂ -CH=CH-C ₆ H ₆	CH ₂	0.5
46	=O	6:OCH ₃	H	CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.5
47	=O	6:OCH ₃	H	CH ₂ -CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.4
48	=O	6:OCH ₃	H	(CH ₂) ₂ -CH-(C ₆ H ₆) ₂	CH ₂	0.7
49	=O	7:OCH ₃	H	(CH ₂) ₂ -c-C ₃ H ₅	CH ₂	0.5
50	=O	7:OCH ₃	H	CH ₂ -c-C ₄ H ₇	CH ₂	0.2
51	=O	7:OCH ₃	H	CH ₂ -c-C ₆ H ₁₁	CH ₂	0.4
52	=O	7:OCH ₃	H	CH ₂ -CH=CH-C ₆ H ₆	CH ₂	0.4
53	=O	7:OCH ₃	H	CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.4
54	=O	7:OCH ₃	H	CH ₂ -CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.3
55	=O	7:OCH ₃	H	(CH ₂) ₂ -CH-(C ₆ H ₆) ₂	CH ₂	0.65

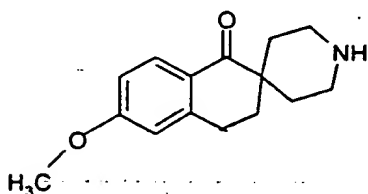
Table 2 (cont.)

Ex.	R ¹ -R ²	R ₃	R ₄	R ₅	A	Rf
56	=O	H	H	(CH ₂) ₂ -c-C ₃ H ₅	CHCH ₃	0.4
57	=O	H	H	CH ₂ -c-C ₄ H ₇	CHCH ₃	0.2
58	=O	H	H	CH ₂ -c-C ₆ H ₁₁	CHCH ₃	0.5
59	=O	H	H	CH ₂ -CH=CH-C ₆ H ₆	CHCH ₃	0.45
60	=O	H	H	CH ₂ -CH ₂ -C ₆ H ₆	CHCH ₃	0.5
61	=O	H	H	CH ₂ -CH ₂ -CH ₂ -C ₆ H ₆	CHCH ₃	0.4
62	=O	H	H	(CH ₂) ₂ -CH-(C ₆ H ₆) ₂	CHCH ₃	0.7
63	=O	6:Cl	H	(CH ₂) ₂ -c-C ₃ H ₅	CH ₂	0.5

-43-

64	=O	6:Cl	H	CH ₂ -c-C ₄ H ₇	CH ₂	0.3
65	=O	6:Cl	H	CH ₂ -c-C ₆ H ₁₁	CH ₂	0.65
66	=O	6:Cl	H	CH ₂ -CH=CH-C ₆ H ₆	CH ₂	0.55
67	=O	6:Cl	H	CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.65
68	=O	6:Cl	H	CH ₂ -CH ₂ -CH ₂ -C ₆ H ₆	CH ₂	0.5
69	=O	6:Cl	H	(CH ₂) ₂ -CH-(C ₆ H ₆) ₂	CH ₂	0.85

EXAMPLE 70

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

The synthesis is similar to the one described in example 1 except in stage 3 wherein 6-methoxytetralone is used instead of 1-tetralone.

N.M.R.: CDCl₃ ¹H ((ppm) Base: 1.9-2.3 (m, 6H); 2.9-3.1 (m, 2H); 3.3-3.6 (m, 4H); 3.85 (s, 3H); 6.65 (s, 1H); 6.8-6.9 (m, 1H); 7.9-8.0 (dd, 1H); 9.5 (bs, 2H)).

M.P. = 236-237°C, TLC (90/10 CH₂Cl₂/MeOH containing 10% NH₄OH): R_f = 0.25.

IR: 2724, 1657, 1595, 1446, 1258, 1223, 1086, 978, 906, 839 cm⁻¹

As noted above, the invention compounds of Formula I are useful for treating chronic pain and other CNS disorders such as seizures, e.g. epilepsy. The compounds have been evaluated in standard assays to measure their ability to block isolated mammalian Na neuronal channels, as well as their ability to antagonize prostaglandin E₂ (PGE₂) production. Both assays are routinely utilized to indicate clinical utility of compounds for treating chronic pain and other CNS disorders (see Tonelian *et al.*, Anesthesiology, 24: 949-951, 1991).

-44-

EXAMPLE 71

Sodium channel [^3H]-batrachotoxin (BTX) binding assay

Cerebral cortices from male Sprague-Dawley rats were homogenized in a glass-
5 Teflon homogenizer in 10 volumes of ice-cold 0.32 M sucrose, 5 mM K_2HPO_4
(pH 7.4 at 4°C). The homogenate was centrifuged at 1000 g. for 10 min, the pellet
was resuspended in the same volume of sucrose and recentrifuged. The pellet was
discarded and the two supernatants resulting from these two centrifugations were
pooled and centrifuged at 20000 g. for 10 min. The resulting pellet was
10 resuspended in a Na-free assay buffer containing 50 mM HEPES, 5.4 mM KCl,
0.8 mM MgSO_4 , 5.5 mM glucose and 130 mM choline chloride (pH 7.4 at 25°C).
Binding assay were initiated by the addition of 150-200 μg synaptosomal protein
to an assay buffer containing 25 μg scorpion venom (Leirus quinquestriatus), 0.1%
BSA and 10 nM [^3H] batrachotoxin (40 Ci/mmol, NEN) in the presence or
15 absence of different concentrations of unlabelled drugs (250 μl final volume). Non-
specific binding was determined in the presence of 0.3 mM veratridine. Reactions
were incubated for 90 min at 25°C and bound ligand was separated from free by
vacuum filtration through Whatman GF/B filters; the filters were washed with 2x5
ml buffer (5 mM HEPES, 1.8 mM CaCl_2 , 0.8 mM MgSO_4 , 130 mM choline
20 chloride, 0.01% BSA ; pH 7.4 at 25°C) and bound ligand was estimated by liquid
scintillation spectrometry.

EXAMPLE 72

25 $^{22}\text{Na}^+$ influx into SK-N-SH neuroblastoma cells

Characterization of Na^+ channels activity is performed using human SK-N-SH
cells in 96-well culture plates. The effect of tested compounds on Na^+ influx
through the Na^+ channels is evaluated under stimulation by veratridine.

-45-

SK-N-SH cells are preincubated for 15 min at 37°C in the presence of test compounds in a 25 mM hepes/Tris pH 7.5 buffer containing 5.4 mM KCl, 0.8 mM MgSO₄, 1.8 mM CaCl₂, 5mM glucose, 0.1% BSA, 140 mM choline chloride.

The influx of Na⁺ is induced by the incubation for 10 min at 37°C of SK-N-SH cells in the presence of test compound and veratridine in the incubation buffer supplemented with 1 µM ouabaine, 10 mM NaCl, 130 mM choline chloride and ²²Na⁺ (Jacques, Y, Fosset, M. and Lazdunski, M., (1978), Molecular properties of the action potential Na⁺ ionophore in neuroblastoma cells. J. Biol. Chem., 253, 7383-7392).

Following this ²²Na⁺ uptake, cells are washed with 0.1 mM MgCl₂. The radioactivity is then measured with a microplate reader (Topcount, Packard) after the addition of a scintillation liquid (Microscint 40, Packard).

The reference compound is tetrodotoxin tested at 7 concentrations ranging from 10⁻¹⁰M to 10⁻⁷ M in order to determine an IC₅₀ value.

EXAMPLE 73

Analgesic activity on chronic hyperalgesia induced by PGE₂ in rats

The test consists in determining the analgesic effect of the test compound in rats by the Randall and Selitto test, in which chronic hyperalgesia has been triggered by intraplantar injection of PGE₂ over 4 days into a leg, according to a protocol adapted from Nakamura-Craig *et al* (Pain, 63: 33-37, 1995).

The study is carried out on batches of 120-140 g Sprague-Dawley rats to which 100 ng of PGE₂ is administered in a volume of 100 µl by the intraplantar route, for 4 consecutive days twice a day; this causes chronic hyperalgesia in the leg from the 5th day, for at least one week. On the day of the test, in the morning, the threshold of reaction to pain is checked by the Randall and Selitto test, and animals whose threshold is >100 arbitrarily defined units are selected. In the afternoon, the measurement is repeated after prior administration by the s.c. route of a solution of the test compound; this administration is carried out 30 min before measuring the pain threshold. For each batch, the analgesic activity (%) is

-46-

calculated from the means of the thresholds measured before and after treatment, as compared with that of the control animals, who received only the vehicle.

The following Table 3 lists the Na channel binding and the analgesic activities of representative compounds of the invention when measured in the foregoing assays.

Table 3: Pharmacological activities

Compound of Example No	[³ H] BTX assay: Na ⁺ channel binding Ki (nM)	²² Na influx IC50 (μM)	PGE ₂ assay: Analgesic activity at 10 mg/kg S.C. (%)
2	876	10.7	49
6	1435	3.4	67
7	366	0.94	57
8	397	0.97	47
10	3890	30	100
33	291	1.2	81
36	475	3.4	51
42	ND	4.3	46
43	ND	6	39
47	ND	0.6	66
49	2183	7.6	38
70	ND	ND	46

The foregoing biological data establish that the compounds of Formula I are particularly useful for treating CNS disorders in mammals, especially neuropathic pain, trigeminal neuralgia, diabetic neuropathy, sciatic neuropathy and seizures. The compounds are particularly well suited to the treatment of diabetic neuropathy, which is the most common complication accompanying diabetes mellitus. The compounds also are useful for prophylaxis and treatment of migraine.

The invention compounds can be administered to humans who are in need of treatment for a chronic pain condition or seizure disorder by both the oral and parenteral routes, for instance as tablets or capsules, or as subcutaneous or intravenous injections. The compounds will be administered in an amount which is effective to control and treat the seizure disorder or relieve the neuropathic pain sensation. Such effective amounts will generally be from about 0.1 to about 2000 mg/kg of mammalian body weight. Commonly prescribed doses will be from about 5 mg/kg to about 500 mg/kg. Such dosage amounts can be administered to adult humans from 1 to 4 times a day for the relief of neuropathic pain and seizure disorders. The precise dose to be employed will depend upon the specific compound of Formula I utilized, the particular condition of the subject being treated, and generally will be dictated by the attending physician or other medical practitioner.

The compounds can be formulated by normal methods for convenient oral or parenteral dosing. Typical oral forms are tablets, capsules, troches, elixirs, syrups, suspensions, and controlled sustained release forms, for example through osmotic pumps. The compounds can likewise be formulated for administration intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. The compounds are formulated by using conventional diluents, excipients, carriers and binders routinely used in the pharmaceutical art. For example, the compounds can be admixed with carriers, diluents and excipients such as starch, cellulose, PVP, methylcellulose, sugar, wax, talc, and with stabilizers and binders such as Mg stearate, MgO, CaCO₃, methyl-*p*-hydroxybenzoate (methylparaben), and *n*-propyl-*p*-hydrobenzoate (propylparaben).

The following additional examples illustrate typical pharmaceutical formulations which are provided by this invention.

EXAMPLE 74

Tablet Preparation

5	Compound of Example 10	25.0 mg
	Microcrystalline cellulose	50.0 mg
	Modified food corn starch	50.0 mg
	Magnesium stearate	1.0 mg

The above ingredients are blended to uniformity and compressed into a tablet.

10 Such tablets are administered at the rate of 1 to 4 times a day to a human suffering from chronic pain.

EXAMPLE 75

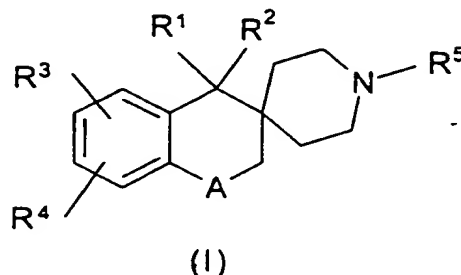
Intravenous Preparation

15	Compound of example 2	400 mg
	Acetate buffer	20 ml
	dil aqueous HCl or NaOH	to pH6.5
	Sterile isotonic saline	qs 1000 ml

20 The invention compound is dissolved in the acetate buffer and the pH is adjusted to 6.5. Isotonic saline is added to a volume of 1000 ml. The solution is filled into a sterile flexible plastic container equipped with a drip tube. The solution is administered IV to a patient suffering from diabetic neuropathy.

What is claimed is :

1. A tricyclic compound of Formula I:



5 wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen or hydroxy; or

R^1 and R^2 together are oxygen ;

A is a bond, CH_2 , CH CH_3 , CH_2 CH_2 or $C(CH_3)_2$;

10 R^3 and R^4 are the same or different and are hydrogen, halo, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, trifluoromethyl, NO_2 , COR^6 , $COOR^6$ or NR^6R^7 , wherein R^6 and R^7 are the same or different and are hydrogen, C_1 - C_6 alkyl or benzyl ;

15 R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, $(O=C)$ - C_{1-6} alkyl, $(O=C)$ - C_{2-6} alkenyl, $(O=C)$ - C_{3-6} cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3 - C_6 cycloalkyl, phenyl or substituted phenyl, and a pharmaceutically acceptable salt thereof.

20 2. A compound according to Claim 1, wherein R^5 is C_1 - C_6 alkyl, optionally substituted with phenyl or a C_3 - C_6 cycloalkyl group.

3. A compound according to Claim 1 or 2, wherein R^3 is hydrogen, halogen or C_{1-4} alkoxy.

4. A compound according to any one of Claims 1 to 3, wherein R¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl or C₃₋₆ cycloalkyl, optionally substituted by 1, 2 or 3 groups selected from halo, C₃₋₆ cycloalkyl, phenyl or substituted phenyl, and R² is hydrogen.

5. A compound according to any one of Claims 1 to 4, wherein R⁴ is hydrogen.

6. A compound selected from the group consisting of:

3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

10 1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

15 1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1H),4'-piperidine];

20 1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

25 1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

- 1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
5 3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;
3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
10 3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;
1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;
15 1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]
1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;
1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
20 6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
25 1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
30 1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

5 1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

10 1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

15 1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

20 1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2'-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

25 1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

30 1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

- 1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 5 1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 10 1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 15 1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 20 1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 25 6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 30 6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

5 3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

7. A compound selected from the group consisting of:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

10 1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1H),4'-piperidine];

15 1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

20 1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

25 1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

30 1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

- 1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 5 1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'- (1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 10 1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 15 1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 20 1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 25 1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;
- 30 1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

- 1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 5 1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 10 1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 15 1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 20 6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;
- 6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and
- 25 6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.
- 3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

8. A compound selected from the group consisting of :

- 1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 30 1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];
- 1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

-57-

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1H),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine];

5 1'-(3-phenylpropyl)-3,4-dihydro-1-oxospiro(naphthalene-2(1H),4'-piperidine);

1'-cyclobutylmethyl-3,4-dihydro-5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine);

1'-cyclopropylethyl-3,4-dihydro-6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine);

10 1'-cyclobutylmethyl-3,4-dihydro-6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine);

1'-(3-phenylpropyl)-3,4-dihydro-6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine);

15 1'-cyclopropylethyl-3,4-dihydro-7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine);

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1H),4'-piperidine]

9. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 8 admixed with a pharmaceutically acceptable carrier, diluent, or carrier therefor.

20

10. A method for treating a mammal suffering from pain and in need of treatment comprising administering an effective amount of a compound of any one of Claims 1 to 8.

25

11. A method according to Claim 10 wherein the pain is neuropathic pain.

12. A method according to Claim 10 wherein the pain is diabetic neuropathy.

-58-

13. A method for treating a mammal suffering from a seizure disorder comprising administering an effective amount of a compound of any one of Claims 1 to 8.

(19)



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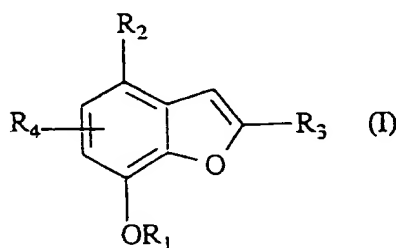
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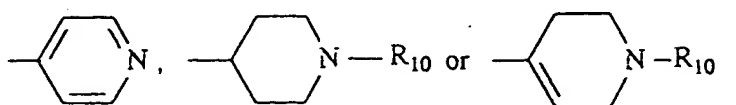
(54) **2-(Piperidin-4-yl, pyridin-4-yl and tetrahydropyridin-4-yl)benzofuran-7-ol and carbamate derivatives, their preparation and their use as acetylcholinesterase inhibitors.**

(57) **2-(piperidin-4-yl, pyridin-4-yl and tetrahydropyridin-4-yl)benzofuran-7-ol and carbamate derivatives of the formula I**



wherein

- R₁ is hydrogen, loweralkyl, arylloweralkyl, CONHR₅ or CONR₆R₇
R₂ is hydrogen, cyano, CH₂NR₈R₉, CONHR₅ or CONR₆R₇;
R₃ is



where R₁₀ is hydrogen, loweralkyl, arylloweralkyl, CONHR₅, CONR₆R₇, acyl, acyloxyloweralkyl or acyloxyarylloweralkyl;

R₄ is hydrogen, halogen, loweralkyl or loweralkoxy;

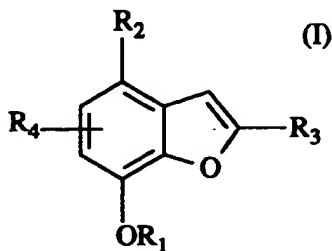
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- R₅ is hydrogen, loweralkyl or arylalkyl;
- R₆ is loweralkyl or arylalkyl;
- R₇ is loweralkyl or arylalkyl;
- R₈ is hydrogen, loweralkyl, arylalkyl or acyl;
- R₉ is hydrogen, loweralkyl or arylalkyl;
- R₁₁ is loweralkyl, aryl or arylalkyl;

with the proviso that if R₁ is hydrogen or loweralkyl, R₂ cannot be hydrogen; or a pharmaceutically acceptable acid addition salt thereof, or where applicable, an optical or geometric isomer or racemic mixture thereof, which are useful as acetylcholinesterase inhibitors and as such may be useful for the treatment of Alzheimer's disease and other senile dementias.

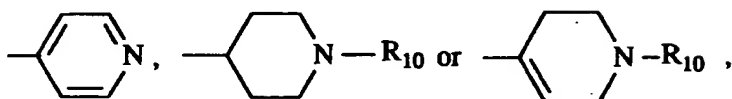
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The present invention relates to compounds of the general formula



wherein

- 15 R_1 is hydrogen, loweralkyl, arylloweralkyl, CONHR_{11} or CONR_6R_7
 R_2 is hydrogen, cyano, $\text{CH}_2\text{NR}_8\text{R}_9$, CONHR_5 or CONR_6R_7 ;
 R_3 is



where R_{10} is hydrogen, loweralkyl, arylloweralkyl, CONHR_5 , CONR_6R_7 , acyl, acyloxyloweralkyl or acylox-
 25 yarylloweralkyl;

- R_4 is hydrogen, halogen, loweralkyl or loweralkoxy;
 R_5 is hydrogen, loweralkyl or arylloweralkyl;
 R_6 is loweralkyl or arylloweralkyl;
 R_7 is loweralkyl or arylloweralkyl;
 30 R_8 is hydrogen, loweralkyl, arylloweralkyl or acyl;
 R_9 is hydrogen, loweralkyl or arylloweralkyl;
 R_{11} is loweralkyl, aryl or arylloweralkyl;
 with the proviso that if R_1 is hydrogen or loweralkyl, R_2 cannot be hydrogen;
 or a pharmaceutically acceptable acid addition salt thereof, or, where applicable,
 35 an optical or geometric isomer or racemic mixture thereof.

Additionally, this invention also relates to novel intermediates encompassed by the above formula, to
 pharmaceutical compositions containing said compounds and to their use as acetylcholinesterase inhibitors.

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification
 and appended claims.

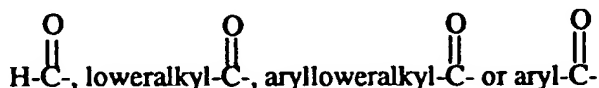
40 The term "lower" shall mean the group it is describing contains from 1 to 6 carbon atoms.

The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 6 carbon atoms,
 e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and straight and branched chain
 pentyl and hexyl.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

45 The term aryl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which is
 independently loweralkyl, loweralkoxy, halogen, trifluoromethyl or nitro.

The term acyl shall mean a group of the formula



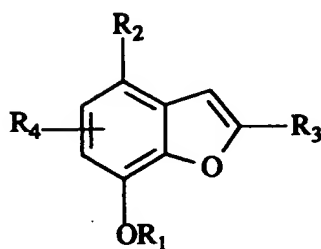
where loweralkyl and aryl are as defined above.

55 Throughout the specification and appended claims, a given chemical formula or name shall encompass
 all stereo and optical isomers where such isomers exist.

Additionally, a given chemical formula or name shall encompass the pharmaceutically acceptable
 addition salts thereof.

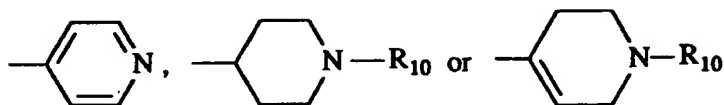
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In a preferred embodiment of this invention are compounds of the formula



where

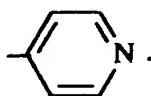
- 15 R₁ is CONHR₁₁ or CONR₆R₇;
 R₂ is CH₂NR₈R₉, CONHR₆ or CONR₆R₇;
 R₃ is



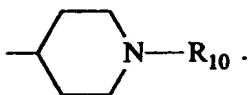
- 25 where R₁₀ is hydrogen or loweralkyl;
 R₄ is hydrogen or halogen;
 R₅ is hydrogen or loweralkyl;
 R₆ is loweralkyl;
 R₇ is loweralkyl;
 30 R₈ is hydrogen or loweralkyl;
 R₉ is hydrogen or loweralkyl; and
 R₁₁ is loweralkyl, aryl or arylloweralkyl.

The following compounds are particularly preferred:

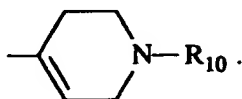
- a. A compound of formula I as defined above wherein R₃ is



- b. A compound of formula I as defined above wherein R₃ is



- c. A compound of formula I as defined above wherein R₃ is



- d. A compound as defined under a) wherein R₁ is CONHR₁₁.

The compound as defined under d) which is 2-(4-pyridinyl)benzofuran-7-yl methyl carbamate.

- f. The compound as defined under d) which is 2-(4-pyridinyl)benzofuran-7-yl butyl carbamate.

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g. A compound as defined under a) wherein R_1 is loweralkyl.

h. The compound as defined under g) which is 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)-benzofuranamide.

i. A compound as defined under b) wherein R_1 is CONHR_{11} .

5 j. The compound as defined under i) which is 2-(1-methyl-4-piperidinyl)-benzofuran-7-yl methyl carbamate.

k. A compound as defined under b) wherein R_1 is CONR_6R_7 .

l. The compound as defined under k) which is 2-(4-piperidinyl)-benzofuran-7-yl dimethyl carbamate.

m. A compound as defined under b) wherein R_1 is loweralkyl.

10 n. The compound as defined under m) which is 1-methyl-4-(4-N,N-diethylamido-7-methoxy-2-benzofuranyl)piperidinium maleate.

o. The compound as defined under m) which is 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)piperidinium maleate.

15 p. The compound as defined under m) which is 1-methyl-4-(4-aminomethyl-7-methoxy-2-benzofuranyl)piperidine.

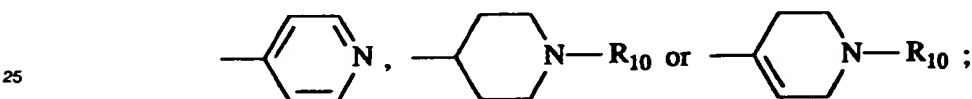
q. The compound as defined under m) which is 1-methyl-4-(4-N,N-diethylaminomethyl-7-methoxy-2-benzofuranyl)piperidine.

Preferred intermediates of this invention are compounds wherein

R_1 is loweralkyl;

20 R_2 is cyano, $\text{CH}_2\text{NR}_8\text{R}_9$ or CONR_6R_7 ;

R_3 is



R_4 is hydrogen;

R_5 is loweralkyl; and

30 R_6 , R_7 , R_8 , R_9 and R_{10} are loweralkyl.

The compounds of this invention are prepared in the following manner. The substituents R_1 to R_{11} are as defined above unless indicated otherwise.

The compounds of this invention can be prepared according to either of the following synthetic routes.

35 SYNTHETIC ROUTE I

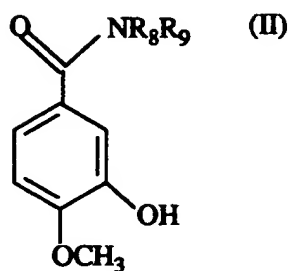
A carboxylic acid of the formula



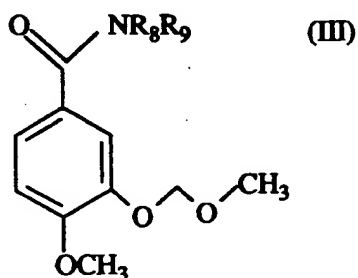
50 is reacted with thionyl chloride, in a suitable solvent such as toluene, and subsequently reacted with a secondary amine of the formula HNR_8R_9 , where R_8 and R_9 are loweralkyl, to yield compound (II) of the formula

55

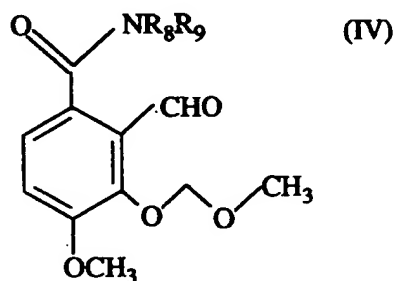
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Compound II is reacted in chloromethyl methyl ether with 50% NaOH in dichloromethane with tetrabutylammonium chloride to afford compound III of the formula

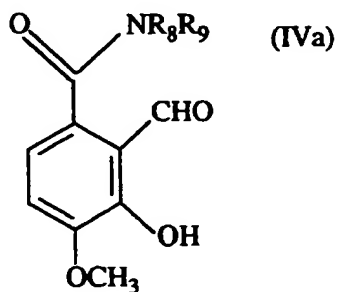


Compound III in THF is subsequently reacted with sec-butyllithium in a suitable solvent such as cyclohexane, and dimethylformamide is added later to afford compound IV of the formula



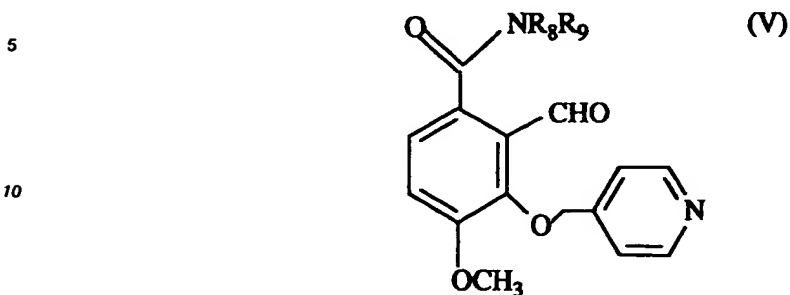
where R_8 and R_9 are ethyl. This reaction is typically conducted at a temperature of -70 to -40°C for 1 to 4 hours.

Compound IV is hydrolyzed by standard means to afford compound IVa of the formula



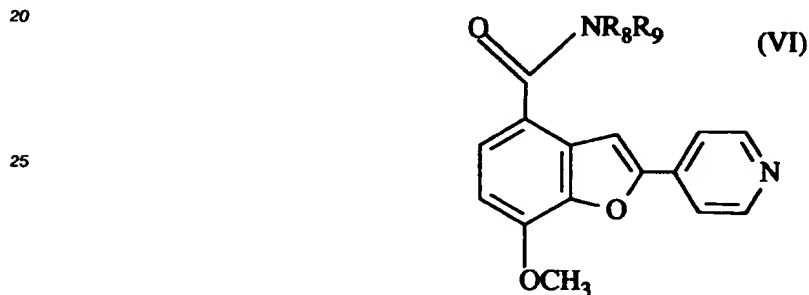
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Compound IVa is reacted with 4-picolylchlorid hydrochlorid, potassium carbonate and a catalyst such as potassium iodide to yield Compound V of the formula



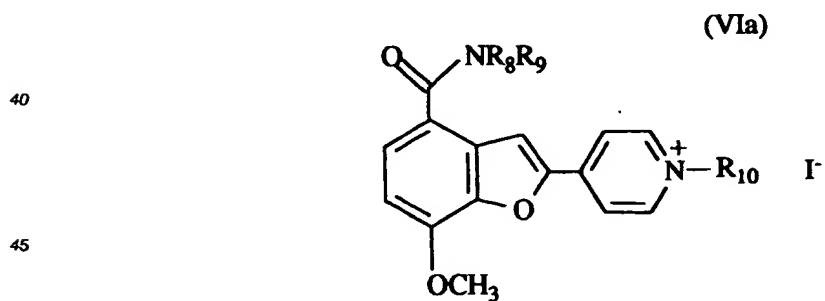
This reaction is typically conducted in a suitable solvent such as dimethylformamide. The reaction mixture is stirred at about 60-100 °C for 1-3 hours and then heated to about 130-170 °C for 10-30 minutes.

Compound VI of the formula



was concomitantly formed in the synthesis of Compound V, and the two compounds were chromatographically separated.

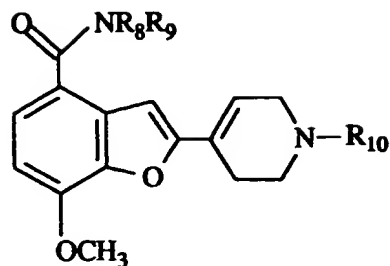
Compound VI is subsequently reacted with methyl iodide in methylethyl ketone or other suitable solvent at a temperature of about 40 to 60 °C to yield Compound VIa of the formula



where R₁₀ is methyl. Compound VIa is then treated with a reducing agent such as sodium borohydride or another metallic borohydride in a loweralkanolic solvent such as methanol to give Compound VIb of the formula

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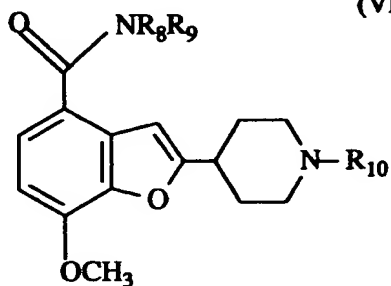
(VIb)



where R_{10} is methyl. This reaction typically takes place at a temperature of about -10 to 100°C for 0.5 to 24 hours.

Compound VIb is subsequently hydrogenated in the presence of a noble metal catalyst and an acid such as hydrogen bromide to prepare compound VII of the formula

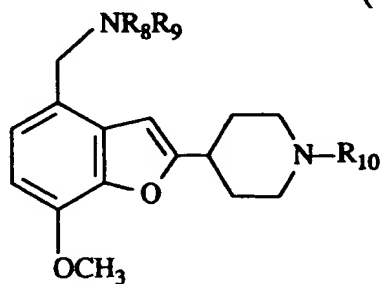
(VII)



where R_{10} is methyl. Preferred noble metal catalysts include palladium, platinum or rhodium. Platinum, in this case, is preferred; in the form of the metal supported on an inert surface such as carbon or as the oxide or salt.

Compound VII is then treated with a reducing agent such as lithium aluminum hydride to yield compound VIII of the formula

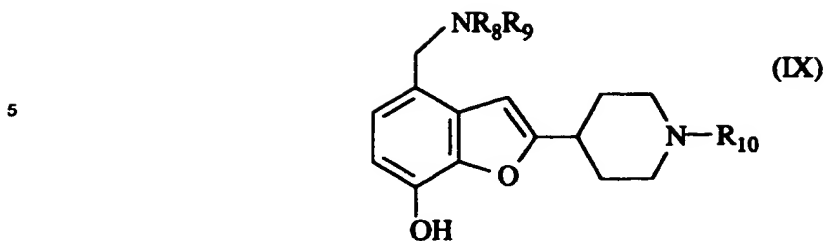
(VIII)



where R_{10} is methyl. This reaction typically takes place in a suitable solvent such as tetrahydrofuran at a temperature of about 40 to 60°C for 2 to 4 hours.

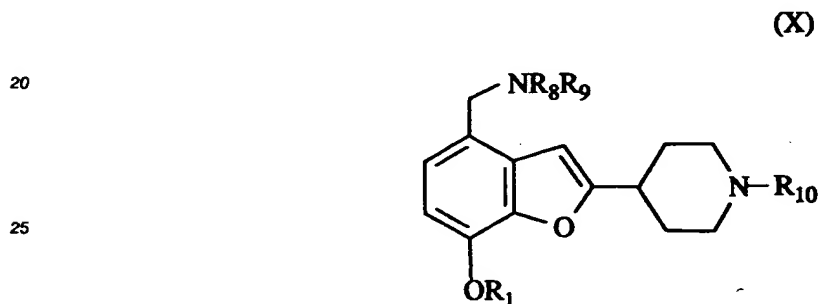
Compound VIII is treated with a strong acid, such as 48% HBr, to yield compound IX of the formula

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where R_{10} is methyl.

Compound IX is subsequently mixed with a catalytic amount of a catalyst such as CuCl or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable solvent such as dimethylformamide to which is added an isocyanate of the formula $R_{11}NCO$, where R_{11} is loweralkyl, aryl or arylloweralkyl or a carbamoyl chloride of the formula $ClCONR_6R_7$ to afford compound X of the formula



30 where R_1 is $CONHR_{11}$ or $CONR_6R_7$. This reaction typically takes place under a nitrogen atmosphere at ambient temperature for 12 to 20 hours.

SYNTHETIC ROUTE II

35 Alternatively, the compounds of this invention can be prepared according to the following synthetic route.

A solution of o-vanillin of the formula



and picolylchloride hydrochloride is reacted with potassium carbonate and potassium iodide in a suitable solvent such as dimethylformamide to afford compound XI of the formula

50

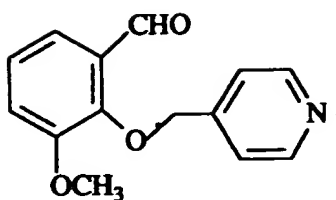
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(XI)

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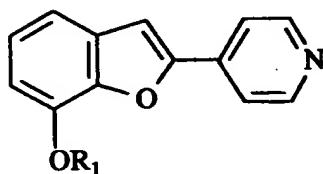


Compound XI is subsequently cyclized by reaction with H_2SO_4 to afford Compound XII of the formula

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(XII)

20



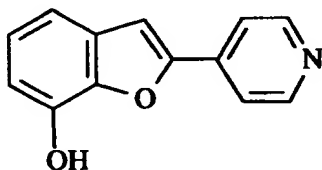
Typically, this reaction takes place in a suitable solvent such as DMF at a temperature of about 120 to 170°C for 6 to 10 hours. Compound XII, where R_1 is loweralkyl, can be reacted with a strong acid such as hydrogen bromide at reflux to prepare compound XIIIa

25

(XIIIa)

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35



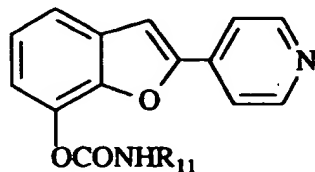
Compound XIIIa is subsequently reacted with an isocyanate of the formula R_{11}NCO , where R_{11} is as defined in the previous synthetic route, to afford compound XIII of the formula

40

(XIII)

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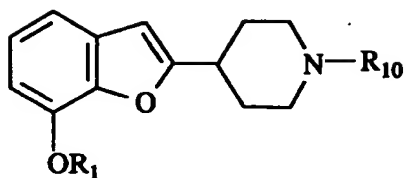
This reaction typically takes place in the presence of a catalytic amount of a metallic halide, such as CuCl or DBU, and ethyl acetate at ambient temperature under nitrogen or other inert gas.

Compound XII, where R_1 is loweralkyl, is reacted as shown in the previous synthetic route to afford the piperidyl compounds of the formula

55

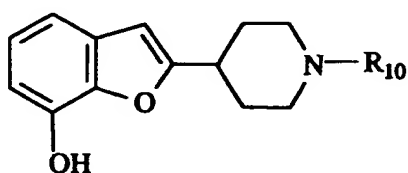
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(XIV)

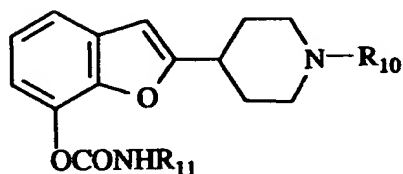


Compound XIV is reacted as previously shown to prepare compounds XIVa and XIVb where R₁ is hydrogen and CONHR₁₁, respectively.

(XIVa)



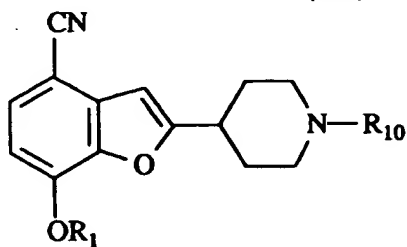
(XIVb)



Alternatively, Compound XIVa can also be reacted with a bicyclic amidine catalyst, such as DBU, with the subsequent addition of an isocyanate of the formula R₁₁NCO to afford compound XIVb. This reaction is typically conducted in a suitable solvent such as acetonitrile under nitrogen at ambient temperature for 2 to 5 hours.

Compound XIV, where R₁ is loweralkyl, is reacted with chlorosulfonylisocyanate under nitrogen to afford Compound XV of the formula

(XV)

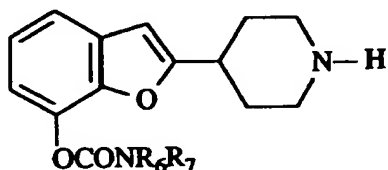


This reaction typically takes place in a suitable solvent such as dichloromethane at room temperature. The reaction mixture is stirred at ambient temperature for 1 to 5 hours and a small portion of dimethylformamide is added and stirring is continued for 12-18 hours.

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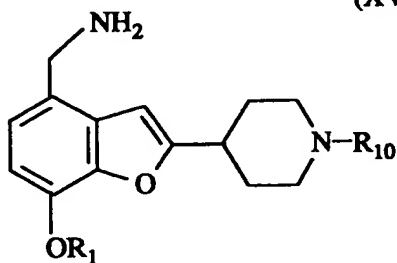
Compound XIVb, where R_{10} is methyl, is reacted with chloroethyl chloroformate in a suitable solvent such as dichloroethane and refluxed for 1 to 12 hours. The mixture is concentrated, then diluted with an alkanolic solvent, such as methanol, and refluxed from 1 to 4 hours to yield compound XIVc of the formula

(XIVc)



Compound XV is treated with lithium aluminum hydride under a nitrogen atmosphere to yield Compound XVI of the formula

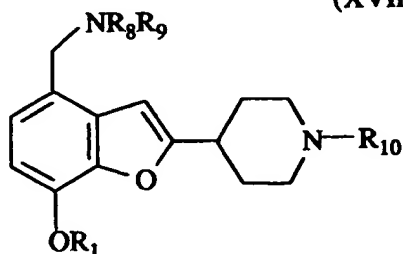
(XVI)



This reaction typically takes place in a suitable solvent such as tetrahydrofuran at ambient temperature for 2 to 6 hours.

Compound XVI can then be treated with a loweralkyl halide or diloweralkyl sulfate to afford Compound XVII of the formula

(XVII)



where R_8 is loweralkyl and R_9 is hydrogen or loweralkyl.

The compounds of the present invention are useful as acetylcholinesterase inhibitors and as such may be useful for the treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with central cholinergic innervation. This same

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innervation is suggested to be weakened in Alzheimer patients. We have determined *in vitro* inhibition of acetylcholinesterase activity in rat striatum according to the method described below.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

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Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in the brain correlates with cholinergic innervation and subfractionation shows the highest level

10 in nerve terminals.

It is generally accepted that the physiological role of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinomimetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AChE inhibitors may also be beneficial in the treatment

15 of Alzheimer's dementia.

The method described below was used in this invention for assaying anticholinesterase activity. This is a modification of the method of Ellman et al., *Biochem. Pharmacol.* 7, 88(1961).

Procedure:

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A. Reagents

1. 0.05 M Phosphate buffer, pH 7.2
 - (a) 6.85 g $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ /100 ml distilled H_2O
 - 25 (b) 13.40 g $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ /100 ml distilled H_2O
 - (c) add (a) to (b) until pH reaches 7.2
 - (d) Dilute 1:10
2. Substrate in buffer
 - (a) 198 mg acetylthiocholine chloride (10 mM)
 - 30 (b) bring to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)
3. DTNB in buffer
 - (a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
 - (b) bring to 100 ml with 0.05M phosphate buffer, pH 7.2 (reagent 1)
4. A 2mM stock solution of the test drug is made up in a suitable solvent and brought to volume with 0.5
- 35 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4}M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation

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Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed and homogenized in 19 volumes (approximately 7 mg protein/ml) of 0.05 M phosphate buffer, pH 7.2, using a Potter-Elvehjem homogenizer. A 25 microliter aliquot of the homogenate is added to 1 ml of vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37°C .

45

C. Assay

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

50

Instrument Settings

Kinetics Soft-Pac Module #598273 (10)
 Program #6 Kindata:
 55 Source - Vis
 Wavelength - 412 nm
 Sipper - none
 Cuvettes - 2 ml cuvettes using auto 6-sampler

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Blank - 1 for each substrate concentration

Interval time - 15 seconds (15 or 30 seconds for kinetics)

Total time - 5 minutes (5 or 10 minutes for kinetics)

Plot - y s

Span - autoscale

Slope - increasing

Results - yes (gives slope)

Factor-1 Reagents are added to the blank and sample cuvettes as follows:

Blank:	0.8 ml Phosphate Buffer/DTNB 0.8 ml Buffer/Substrate
Control:	0.8 ml Phosphate Buffer/DTNB/Enzyme 0.8 ml Phosphate Buffer/Substrate
Drug:	0.8 ml Phosphate Buffer/DTNB/Drug/Enzyme 0.8 ml Phosphate Buffer/Substrate

Blank values are determined for each run to control non-enzymatic hydrolysis of substrate and these values are automatically subtracted by the kindata program available on kinetics soft-pac module. This program also calculates the rate of absorbance change for each cuvette.

For IC₅₀ Determinations:

Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration

$$\% \text{ Inhibition} = \left(\frac{\text{slope control} - \text{slope drug}}{\text{slope control}} \right) (100)$$

IC₅₀ values are calculated from log-probit analysis. Results of this assay for some of the compounds of this invention and a reference compound are presented below in Table 1.

TABLE 1

Compound	Inhibitory Concentration (μ M) Brain AChE
2-(1-methyl-4-piperidinyl)benzofuran-7-yl methyl carbamate	1.8
2-(4-pyridinyl)benzofuran-7-yl methyl carbamate	1.2
2-(1-methyl-4-piperidinyl)benzofuran-7-yl diethyl carbamate	1.9
Physostigmine (reference)	0.006

These compounds are administered to a subject who may benefit from the administration of acetylcholinesterase inhibitors at an effective oral, parenteral or intravenous dose of from about 1 to 100 mg/kg of body weight per day. A particularly preferred effective amount is about 10 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimen should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the compound. It is to be further understood that the dosages set forth herein are exemplary only and do not to any extent limit the scope or practice of the invention.

Effective quantities of the compounds of the present invention may be administered to a subject by any one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

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Preferred pharmaceutically acceptable addition salts include salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids; as well as organic acids such as tartaric, citric, acetic, succinic, malic, fumaric, and oxalic acids.

The active compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 4% to about 75% of the weight of the unit. The amount of compound present in such composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 mgs of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel™, corn starch and the like; a lubricant such as magnesium stearate or Sterotex®; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the aforesaid compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 mgs of active compound.

The solutions or suspensions may also include the following components; a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Examples of possible pharmaceutical formulations such as tablets, suppositories and emulsions are described below:

PHARMACEUTICAL FORMULATIONS

TABLET:

Ingredients	In each tablet
Active ingredient	300 mg
Polyvinylpyrrolidone	22.5 mg
Lactose	61.75 mg
Alcohol 3A - 200 proof	4.5 mg
Stearic acid	9 mg
Talc	13.5 mg
Corn starch	43.25 mg

Blend the active compound, polyvinylpyrrolidone and lactose together and pass through a 40-mesh screen. Add the alcohol slowly, knead well; screen the wet mass through a 4-mesh screen and dry the granulation at 50°C overnight. Screen the dried granulation through a 20-mesh screen. Bolt the stearic acid,

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talc and corn starch through a 60-mesh screen prior to mixing by tumbling with the granulation. Compress using 7/16 in. standard concave punch. 10 tablets should weigh 4.5 g.

SUPPOSITORY:

Ingredients	In each suppository
Active ingredient	300 mg
Glycerin	3000 mg
Purified water	200 mg

The glycerin is heated in a suitable container to about 120°C. The drug is dissolved, with gentle stirring, in the heated glycerin after which the purified water is added, mixed and the hot mixture immediately poured into a suitable mold.

EMULSION:

Ingredients	Amount
Gelatin Type A*	4 g
Active Ingredient	360 mg
Flavor as desired	
Alcohol	30 ml
Oil	250 ml
Purified water, to make	500 ml

* prepared from acid-treated precursors; used at a pH of ca. 3.2.

Add the gelatin and the drug to about 300 ml of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°C, and maintain this temperature for about 20 min. Cool to 50°C, add the flavor, the alcohol, and sufficient purified water to make 500 ml. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is completely and uniformly dispersed.

Examples of the compounds of this invention include: N,N-Diethyl-2-formyl-4-methoxy-3-(methoxymethylenoxy)benzamide; N,N-diethyl-4-methoxy-2-formyl-3-(4-pyridinylmethoxy)benzamide; 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)benzofuranamide; 1-methyl-4-(4-N,N-diethylamido-7-methoxy-2-benzofuranyl)piperidinium maleate; 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)piperidinium maleate; 1-methyl-4-(4-aminomethyl-7-methoxy-2-benzofuranyl)piperidine dihydrobromide; 1-methyl-4-(4-N,N-diethylaminomethyl-7-methoxy-2-benzofuranyl)piperidine dihydrobromide monohydrate; 2-(1-methyl-4-piperidinyl)-benzofuran-7-yl methyl carbamate; 2-(4-pyridinyl)benzofuran-7-yl methyl carbamate; 2-(4-pyridinyl)benzofuran-7-yl butyl carbamate; Methyl-4-(7-methoxy-2-benzofuranyl)piperidine; 1-methyl-4-(4-N,N-dimethylamino-7-methoxy-2-benzofuranyl)piperidine; 2-(1-methyl-4-piperidinyl)benzofuran-7-yl 1,2,3,4-tetrahydroisoquinolyl carbamate; 2-(4-pyridinyl)-4-N,N-diethylaminobenzofuran-7-yl methyl carbamate; 2-(1-methyl-4-piperidinyl)-4-N,N-dimethylamino-2-benzofuran-7-yl butyl carbamate; and 2-(4-piperidinyl)-benzofuran-7-yl dimethyl carbamate.

The following examples are for illustrative purposes and are not to be construed as limiting the invention disclosed therein. All temperatures are given in degrees centigrade (°C) unless indicated otherwise.

EXAMPLE 1

N,N-DIETHYL-2-FORMYL-4-METHOXY-3-(METHOXYMETHYLENOXY)BENZAMIDE

To a solution of N,N-diethyl-4-methoxy-3-(methoxymethylenoxy)benzamide (82.0 g) in tetrahydrofuran (hereafter "THF") (800 ml) at -55°C was added a 1.3 M solution of sec-butyl lithium in cyclohexane (307

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ml) dropwise during 1 hour. After stirring the mixture for an additional hour at -55 °C, dimethylformamide (hereafter "DMF"), (36.5 g) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 2 hours, poured into ice cold 5% HCl, and extracted twice with ethyl acetate. The combined organic phases were washed with water and brine, dried (Na₂SO₄) and concentrated *in vacuo* to give 97g of crude product. Preparative high performance liquid chromatography (silica gel, eluting with 1:2 heptane:ethyl acetate) afforded 58 g of the pure product which was crystallized from heptane/acetone, m.p. 75-77 °C.

10

Analysis:			
Calculated for C ₁₅ H ₂₁ NO ₅ :	61.00%C	7.17%H	4.74%N
Found:	60.97%C	7.12%H	4.84%N

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EXAMPLE 2a**N,N-DIETHYL-4-METHOXY-2-FORMYL-3-(4-PYRIDINYLMETHOXY)BENZAMIDE**

A suspension of N,N-diethyl-4-methoxy-3-(4-pyridinylmethoxy)benzamide (19.0g), 4-picolychloride hydrochloride (15.0 g), K₂CO₃ (60.0 g) and potassium iodide (5.0 g) in DMF (500 ml) was stirred at 80 °C for 2 hours and then heated to 150 °C for 15 minutes. After cooling to room temperature, the mixture was poured into 3 l of water, and extracted twice with ethyl acetate. The combined organic phases were washed with 5% Na₂CO₃, dried (Na₂SO₄) and concentrated *in vacuo*. High performance liquid chromatography (silica gel, eluting with 1:1 heptane:ethyl acetate) afforded 6.5 g of the product which was crystallized from heptane/acetone, m.p. 117-118 °C.

30

Analysis:			
Calculated for C ₁₉ H ₂₂ N ₂ O ₄ :	66.65%C	6.48%H	8.18%N
Found:	66.56%C	6.64%H	8.12%N

EXAMPLE 2b

35

4-(N,N-DIETHYL)-7-METHOXY-2-(4-PYRIDINYL)BENZOFURANAMIDE

The named compound was produced during the reaction leading to the formation of the N,N-diethyl-4-methoxy-2-formyl-3-(4-pyridinylmethoxy)benzamide and was isolated in pure form in the chromatography step. Crystallization from heptane/acetone afforded 2.8 g of the named compound, m.p. 115-117 °C.

45

Analysis:			
Calculated for C ₁₉ H ₂₀ N ₂ O ₃ :	70.35%C	6.21%H	8.64%N
Found:	69.97%C	6.30%H	8.48%N

EXAMPLE 3

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1-METHYL-4-(4-N,N-DIETHYLAMIDO-7-METHOXY-2-BENZOFURANYL)PIPERIDINIUM MALEATE

A mixture of 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)benzofuranamide (4.3 g), methyl iodide (2.55 g) and 2-butanone (30 ml) was stirred at 50 °C for 15 hours. The mixture was cooled to 0 °C, filtered and the resulting solid was washed with cold 2-butanone and heptane to give 4-[2-(4-diethylamido-7-methoxy-2-benzofuranyl)]-1-methyl pyridinium iodide. The quaternary salt (6.0 g) was dissolved in methanol (100 ml) and a solution of NaBH₄ (5.0 g) in H₂O (20 ml) was added dropwise over 30 minutes. The mixture was stirred at ambient temperature for 16 hours, concentrated and the residual aqueous layer was extracted with dichloromethane (hereinafter "DCM"). The DCM extracts were combined, washed with brine and con-

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centrated to give N,N-diethyl-7-methoxy-2-(1-methyl-1,2,3,6-tetrahydro-4-pyridinyl)benzofuranamide.

To a solution of N,N-diethyl-7-methoxy-2-(1-methyl-1,2,3,6-tetrahydro-4-pyridinyl)benzofuranamide (4.4 g) in methanol (120 ml) and 48% HBr (2.1 g) was added PtO₂ (160 mg) and the mixture was hydrogenated in a Parr Shaker for 6 hours at room temperature. The mixture was filtered and the methanol was evaporated *in vacuo*. The residual solution was treated with 2N NH₄OH and extracted twice with DCM. The combined organic phases were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 5% MeOH/DCM containing 0.1% NH₄OH) afforded 2.1 g of product which was converted to the maleic acid salt in ethereal solution, m.p. 123-125 °C.

Analysis:			
Calculated for C ₂₄ H ₃₂ N ₂ O ₇ :	62.59%C	7.00%H	6.08%N
Found:	61.76%C	6.94%H	5.79%N

EXAMPLE 4

1-METHYL-4-(4-CYANO-7-METHOXY-2-BENZOFURANYL)PIPERIDINIUM MALEATE

To a solution of 1-methyl-4-(7-methoxy-2-benzofuranyl)piperidine (2.45 g) in anhydrous DCM under nitrogen was added chlorosulfonylisocyanate (2.2 g) dropwise via syringe at room temperature. The mixture was stirred at ambient temperature for 3 hours, then DMF (0.5 ml) was added, and the mixture was stirred for 15 hours. The reaction mixture was poured into water, and extracted twice with DCM. The combined organic phases were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (silica gel eluting with 5% MeOH/DCM containing 0.01% NH₄OH) afforded 1.55 g of product which was converted to the maleic acid salt in ethereal solution, m.p. 175-177 °C.

Analysis:			
Calculated for C ₂₀ H ₂₂ N ₂ O ₆ :	62.17%C	5.74%H	7.25%N
Found:	61.87%C	5.75%H	7.03%N

EXAMPLE 5

1-METHYL-4-(4-AMINOMETHYL-7-METHOXY-2-BENZOFURANYL)PIPERIDINE DIHYDROBROMIDE

To 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)piperidine (2.7 g) in anhydrous THF under nitrogen was added LiAlH₄ (30 ml of a 1 M solution in THF) dropwise at room temperature. The mixture was stirred at ambient temperature for 4 hours, and then water (2.0 ml) was added slowly under ice cooling. The precipitate was filtered and washed with ethyl acetate. The combined filtrates were dried (Na₂SO₄) and concentrated *in vacuo* to give 2.3 g of the crude product. Flash chromatography (silica gel, eluting with 20% MeOH/DCM + 0.1% NH₄OH) afforded the product, which was converted to the dihydrobromide salt in ethereal solution, m.p. 195 °C (dec.).

Analysis:			
Calculated for C ₁₆ H ₂₄ Br ₂ NO ₂ :	44.06%C	5.55%H	6.42%N
Found:	43.74%C	5.66%H	6.17%N

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EXAMPLE 6**1-METHYL-4-(4-N,N-DIETHYLAMINOMETHYL-7-METHOXY-2-BENZOFURANYL)PIPERIDINE
DIHYDROBROMIDE MONOHYDRATE**

5 To N,N-diethyl-7-methoxy-2-(1-methyl-4-piperidiny)benzofuranamide (2.1 g) in anhydrous THF (20 ml) at room temperature was added a 1 M LiAlH₄ solution in THF (6 ml) dropwise via syringe. The mixture was then heated to 50 °C for 3 hours and after cooling, water (0.5 ml) was carefully added. The mixture was filtered and the filter cake washed twice with ethyl acetate. The combined filtrates were dried (Na₂SO₄) and concentrated *in vacuo* to leave 1.7 g of an oil. To a solution of the oil in DCM was added an HBr solution in diethyl ether at room temperature. The resulting precipitate was filtered, washed with diethyl ether and crystallized from DCM, m.p. 226-229 °C (dec.).

15	Analysis:			
	Calculated for C ₂₀ H ₃₀ N ₂ O ₂ • 2HBr • H ₂ O:	47.07%C	6.72%H	5.49%N
	Found:	46.78%C	6.67%H	5.33%N

EXAMPLE 7**2-(1-METHYL-4-PIPERIDINYL)-BENZOFURAN-7-YL METHYL CARBAMATE**

25 A mixture of 1-methyl-4-(7-methoxy-2-benzofuranyl)piperidine (5.6 g) and 48% HBr (40 ml) was stirred at 120 °C for 30 minutes. After cooling to room temperature, the mixture was neutralized with 10% sodium hydroxide solution and extracted with 1:1 ethyl acetate/1-butanol. The organic extract was washed with brine, concentrated and the resulting oil was chromatographed (silica gel, eluting with 20% MeOH/DCM and 0.5% NH₄OH) to afford 1.9 g of 1-methyl-4-(7-hydroxy-2-benzofuranyl)piperidine.

30 To a mixture of 1-methyl-4-(7-hydroxy-2-benzofuranyl)piperidine (1.8 g) and a catalytic amount of CuCl in DMF (30 ml) was added methylisocyanate (0.7 ml) at room temperature under N₂. The mixture was then stirred for 16 hours at ambient temperature. Water and brine were added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 10% MeOH/DCM + 0.2% NH₄OH) afforded the product, which was crystallized from ethyl acetate, m.p. 144-146 °C.

35	Analysis:			
	Calculated for C ₁₆ H ₂₀ N ₂ O ₃ :	66.65%C	6.99%H	9.72%N
40	Found:	66.53%C	7.04%H	9.69%N

EXAMPLE 8**2-(4-PYRIDINYL)BENZOFURAN-7-YL METHYL CARBAMATE**

45 A mixture of 4-(7-methoxy-2-benzofuranyl)pyridine (5.0 g) and 48% HBr (50 ml) was stirred at 120 °C for 1 hour. The mixture was cooled to room temperature, neutralized with 10% NaOH and 5% Na₂CO₃ and extracted with ethyl acetate. The organic extract was washed with brine and concentrated to give 4-(7-hydroxy-2-benzofuranyl)pyridine.

50 To a mixture of 4-(7-hydroxy-2-benzofuranyl)pyridine (2.0 g) and a catalytic amount of CuCl in DCM (10 ml) and ethyl acetate (20 ml) was added methylisocyanate (1.0 ml) at room temperature under N₂. The mixture was stirred at ambient temperature for 16 hours, diluted with methanol, filtered through Al₂O₃ and concentrated *in vacuo* to give 2.0 g of the crude product which was crystallized from ethyl acetate, m.p. 158-160 °C.

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Analysis:			
Calculated for $C_{15}H_{12}N_2O_3$:	67.16%C	4.51%H	10.44%N
Found:	67.20%C	4.22%H	10.29%N

EXAMPLE 9**4-(7-METHOXY-2-BENZOFURANYL)-PYRIDINE**

To a solution of o-vanillin (6.0 g) and 4-picolychloride hydrochloride (6.6 g) in DMF (70 ml) was added potassium carbonate (20.0 g) and potassium iodide (2.0 g). The mixture was stirred vigorously for 8 hours at 150 °C. The mixture was filtered hot and the filter cake was washed with ethyl acetate. The organic phases were combined and concentrated *in vacuo* to a volume of about 10 ml, poured into water and extracted twice with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 1:2 heptane:ethyl acetate) afforded 2.5 g of the product, which was crystallized from heptane/ethyl acetate, m.p. 140-141 °C.

Analysis:			
Calculated for $C_{14}H_{11}NO_2$:	74.65%C	4.92%H	6.22%N
Found:	74.67%C	4.73%H	6.09%N

EXAMPLE 10**2-(4-PYRIDINYL)BENZOFURAN-7-YL BUTYL CARBAMATE**

To a mixture of 4-(7-hydroxy-2-benzofuranyl)pyridine (1.1 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (150.0 mg) in acetonitrile (20 ml) was added n-butylicocyanate (0.5 g) at room temperature under N_2 . The mixture was then stirred at ambient temperature for 3 hours. The crude product which precipitated out of the reaction mixture was filtered and crystallized from ethyl acetate, then chromatographed silica gel, 2:1 heptane/acetone) to remove residual impurities. Concentration of the appropriate fractions afforded the product, m.p. 140 °C.

Analysis:			
Calculated for $C_{18}H_{18}N_2O_3$:	69.66%C	5.85%H	9.03%N
Found:	69.27%C	5.42%H	8.96%N

EXAMPLE 11**1-METHYL-4-(7-METHOXY-2-BENZOFURANYL)PIPERIDINE**

A mixture of 4-(7-methoxy-2-benzofuranyl)pyridine (66 g), methyl iodide (56.7 g) and 2-butanone (800 ml) was stirred at 50 °C for 4 hours, cooled to room temperature, filtered and the resulting solid was washed with 2-butanone to provide 1-methyl-4-(7-methoxy-2-benzofuranyl)pyridinium iodide, m.p. 225-227 ° (dec.). The quaternary salt (90 g) was dissolved in methanol (1 l) and a solution of $NaBH_4$ (40 g) in H_2O (250 ml) was added dropwise. The mixture was stirred at ambient temperature for 3 hours, concentrated and the residual aqueous layer was extracted with DCM. The extracts were combined, washed with brine and concentrated to give 1 methyl-4-(7-methoxy-2-benzofuranyl)-1,2,3,6-tetrahydropyridine.

A mixture of 1-methyl-4-(7-methoxy-2-benzofuranyl)-1,2,3,6-tetrahydropyridine (58.0 g), methanol (1.5 l), water (200 ml), 48% HBr (42.0 g), and platinum dioxide were shaken under hydrogen at room temperature for 6 hours. The mixture was filtered; the filtrate was concentrated *in vacuo* to the aqueous phase, neutralized with 5% Na_2CO_3 and extracted with CH_2Cl_2 . The organic phase was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give 59 g of the crude product, which was crystallized from

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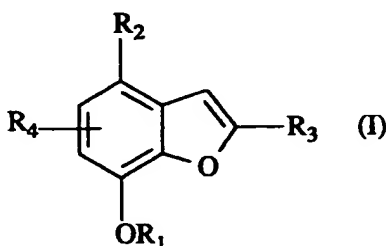
Analysis:			
Calculated for C ₁₅ H ₁₇ NO ₂ :	73.44%C	7.81%H	5.71%N
Found:	73.47%C	7.83%H	5.65%N

2-(4-PIPERIDINYL)BENZOFURAN-7-YL DIMETHYL CARBAMATE HEMIFUMARATE

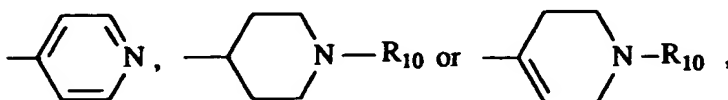
To a suspension of 2-(1-methyl-piperidin-7-yl)benzofuran-7-yl dimethyl carbamate (1.0 g) in dichloroethane (10 ml) was added chloroethyl chloroformate (0.47 g) and the mixture was refluxed for 3 hours. After stirring at room temperature overnight, an additional 0.95 gram of 2-chloroethyl chloroformate was added and the mixture refluxed for 6 hours. The mixture was concentrated, 10 ml of methanol was added and the mixture was heated to reflux for 2 hours. After concentration, the residue was chromatographed (silica gel, 10% MeOH/CH₂CH₂ containing 0.5% NH₄OH) and the fractions were evaporated. The product was dissolved in ethyl acetate and a solution of fumaric acid in ether was added; the resulting solid was collected and dried, m.p. 195-196° C.

Analysis:			
Calculated for: C ₁₈ H ₂₂ N ₂ O ₅	62.42% C	6.40% H	8.09% N
Found:	62.25% C	6.38% H	7.98% N

1. A compound of the formula I



R₁ is hydrogen, loweralkyl, arylloweralkyl, CONHR₁₁, or CONR₆R₇
R₂ is hydrogen, cyano, CH₂NR₈R₉, CONHR₅ or CONR₆R₇;
R₃ is



where R_{10} is hydrogen, loweralkyl, arylloweralkyl, $CONHR_5$, $CONR_6R_7$, acyl, acyloxyloweralkyl or

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acyloxyaryllow ralkyl;

R_4 is hydrogen, halogen, loweralkyl or loweralkoxy;

R_5 is hydrogen, loweralkyl or aryloweralkyl;

R_6 is low ralkyl or arylow ralkyl;

R_7 is loweralkyl or aryloweralkyl;

R_8 is hydrogen, loweralkyl, aryloweralkyl or acyl;

R_9 is hydrogen, loweralkyl or aryloweralkyl;

R_{11} is loweralkyl, aryl or aryloweralkyl;

with the proviso that if R_1 is hydrogen or loweralkyl, R_2 cannot be hydrogen;

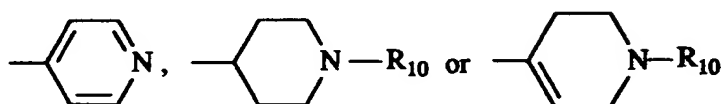
or a pharmaceutically acceptable acid addition salt thereof, or, where applicable, an optical or geometric isomer or racemic mixture thereof.

2. A compound of formula I as defined in claim 1, where

R_1 is CONHR_{11} or $\text{CONR}_6 R_7$;

R_2 is $\text{CH}_2 \text{NR}_8 R_9$, CONHR_5 or $\text{CONR}_6 R_7$;

R_3 is



where R_{10} is hydrogen or loweralkyl;

R_4 is hydrogen or halogen;

R_5 is hydrogen or loweralkyl;

R_6 is loweralkyl;

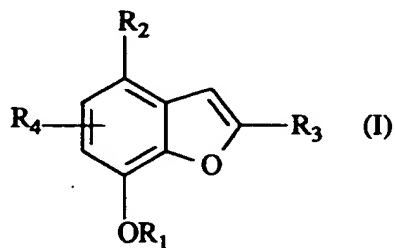
R_7 is loweralkyl;

R_8 is hydrogen or loweralkyl;

R_9 is hydrogen or loweralkyl; and

R_{11} is loweralkyl, aryl or aryloweralkyl.

3. A compound of the formula I

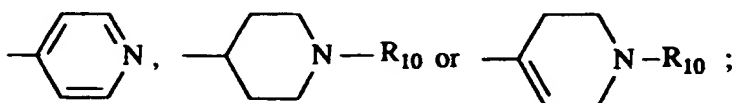


wherein

R_1 is loweralkyl;

R_2 is cyano, $\text{CH}_2 \text{NR}_8 R_9$ or $\text{CONR}_6 R_7$;

R_3 is



R_4 is hydrogen;

R_5 is loweralkyl;

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R₆, R₇, R₈, R₉ and R₁₀ are loweralkyl.

4. A pharmaceutical composition which comprises an effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

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5. The use of a compound as claimed in claims 1 or 2 as a pharmaceutical.

6. The use of a compound as claimed in claim 1 or 2 for the production of a pharmaceutical having an activity as anticholinesterase inhibitor.

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EUROPEAN SEARCH REPORT

Application Number
EP 94 11 1962

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 338 782 (MERCK FROSST CANADA INC.) 25 October 1989 * claim 1 * ---	1,4,5	C07D405/04 C07D307/86 A61K31/44 A61K31/445
X	EP-A-0 165 810 (MERCK FROSST CANADA INC.) 27 December 1985 * claim 1 * ---	1,4,5	
X	US-A-4 210 655 (SCHENKER ET AL.) 1 July 1980 * claims 1-4 * ---	1,5	
A	* see examples 3,14,21 and 27 * ---	1	
Y	EP-A-0 468 187 (EISAI CO., LTD.) 29 January 1992 * see examples 49, 59 and 65 * * page 15 - page 17; claims 1-6,10,11 * ---	1-6	
Y	EP-A-0 296 560 (EISAI CO., LTD.) 28 December 1988 * see example 28 * * page 31 - page 33; claims 1-9,12-15 * ---	1-6	
Y	EP-A-0 259 621 (A/S FERROSAN) 16 March 1988 * see examples 6,7,8,16d,28,29,39 and 40 * * claims 1,4 * ---	1-6	
A	EP-A-0 542 671 (CIBA-GEIGY AG) 19 May 1993 * see formulae VIIa, VIIb and VIIc, page 7 and formula XII, page 10 * * claims 18,29,30 * ---	1-5	
A	EP-A-0 398 413 (DUPHAR INTERNATIONAL RESEARCH B.V.) 22 November 1990 * see compounds 1,2,10,12,14,37,40,42 and 43 * * claim 1 * --- -/--	1-5	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 19 September 1994	Examiner Hartrampf, G
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	

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EUROPEAN SEARCH REPORT

Application Number
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP-A-0 217 530 (ELI LILLY AND COMPANY) 8 April 1987 * claim 1 *	1-5	
A	EP-A-0 006 524 (CIBA-GEIGY AG) 9 January 1980 * the whole document *	1-5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 19 September 1994	Examiner Hartrampf, G
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